IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re	:	U.S. Patent No. 5,590,645
Issued	:	January 7, 1997
Inventors	:	Michael B. Davies, David J. Hearne, Paul K. Rand and Richard I. Walker
Assignee	:	Glaxo Group Limited
For	:	INHALATION DEVICE

Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Applicant, Glaxo Wellcome Inc., a corporation of the State of North Carolina (formerly Glaxo Inc.) represents that it is a subsidiary of Glaxo Group Limited, a company incorporated in England, and agent thereof for purposes of filing this Application for Extension of Patent Term for U.S. Patent 5,590,645 pursuant to a grant of Power of Attorney. See EXHIBIT 1. Applicant further represents pursuant to 35 U.S.C. § 156(d)(1), that Glaxo Group Limited is the record owner and assignee of the entire interest in and to Letters Patent of the United States of America No. 5,590,645 granted to Michael B. Davies, David J. Hearne, Paul K. Rand and Richard I. Walker for INHALATION DEVICE recorded in the United States Patent and Trademark Office on March 15, 1991, Reel 5645, Frame 0202. See EXHIBIT 2.

Applicant further represents, pursuant to 37 C.F.R. § 1.785(d), that it is the holder of the regulatory approval granted by the Food and Drug Administration ("FDA") for SEREVENT DISKUS® (salmeterol xinafoate inhalation powder) for Oral Inhalation Only (hereinafter SEREVENT DISKUS®). See EXHIBIT 3.

Applicant hereby presents this Application for Extension of Patent Term under 35 U.S.C §156 according to the format set forth in 37 C.F.R. § 1.740(a).

(1) This application for extension is based upon the regulatory review period before the FDA of Applicant's Approved Product, SEREVENT® DISKUS®. Specifically, Applicant is seeking to extend U.S. 5,590,645 based upon the approval of the DISKUS® Inhalation Device, not the active ingredient of the drug product, salmeterol xinafoate. A copy of the package insert approved by the FDA as part of New Drug Application ("NDA") 20-692 for the Approved Product is attached hereto as EXHIBIT 4. Identification of the Approved Product, SEREVENT® DISKUS®, is provided as follows:

(a) The DISKUS® Inhalation Device is a specially designed plastic apparatus containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50 mcg of salmeterol as the xinafoate in 12.5 mg of formulation containing lactose. When a blister containing medication is opened by activating the device, the medication is dispersed into the air stream created when the patient inhales through the mouthpiece. See EXHIBIT 4.

(b) Schematic diagrams of the DISKUS® Inhalation Device are provided under EXHIBIT 5.

(2) The Approved Product, SEREVENT® DISKUS®, was subject to regulatory review under Federal Food, Drug and Cosmetic Act, section 505 (21 U.S.C. § 355).

(3) Applicant seeks an extension of patent term for the human drug product, SEREVENT® DISKUS®. On September 19, 1997, Applicant received permission from the FDA under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the commercial marketing or use of SEREVENT® DISKUS®.

(4) The DISKUS® Inhalation Device has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act. The active ingredient of SEREVENT® DISKUS® , salmeterol xinafoate, was previously approved on February 4, 1994 for marketing under the Federal Food Drug and Cosmetic Act as SEREVENT® (salmeterol xinafoate) Inhalation Aerosol (NDA 20-236). However, the active ingredient of SEREVENT® DISKUS® , salmeterol xinafoate, is not being relied upon as the basis for extending U.S. 5,590,645.

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60 day period, beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use, September 19, 1997 and ending 60 days therefrom, November 17, 1997.

(6) The complete identification of the patent for which extension of term is being sought is as follows:

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Assignee	:	Glaxo Group Limited
For	:	INHALATION DEVICE

(7) A complete copy of the patent identified in paragraph (6) above is appended hereto as EXHIBIT 6.

(8) No certificate of correction, disclaimer nor reexamination certificate exists in respect of U.S. Patent 5,590,645. The due date for the first maintenance fees has not arrived to date.

(9) United States Patent Number 5,590,645 claims the inhalation device, *i.e.*, the DISKUS® Inhalation Device, used to administer the active ingredient (salmeterol xinafoate) of the Approved Product SEREVENT® DISKUS®. Applicant hereinbelow lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the Approved Product. See EXHIBITS 4, 5 and 6.

(a) Claim 1 reads as follows:

An inhalation device for use with a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are spaced along the length of and defined between two peelable sheets secured to each other, said inhalation device comprising:

an opening station for receiving a container of a medicament pack being used with said inhalation device;

means positioned to engage peelable sheets of a container which has been received in said opening station for peeling apart the peelable sheets, to open such a container;

an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container; and

indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device.

Claim 1 reads on the Approved Product being that:

the Approved Product, SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) for Oral Inhalation Only provides for the dispensing of the Drug Substance via an Inhalation Device, *i.e.*, the DISKUS® Inhalation Device, wherein the Inhalation Device contains a Coiled Strip having individual Pockets containing the Drug Substance in powder form, the pockets being equidistantly spaced along the length of the Coiled Strip and wherein the Coiled Strip is formed by securing two Sheets together in such a way that they may be peeled apart during operation of the Inhalation Device, (See EXHIBIT 5, Figure E6);

the Approved Product contains a chamber for holding the Coiled Strip containing the Drug Substance, the chamber being formed by the Body Base, Manifold and Body Top, (See EXHIBIT 5, Figures E6 & E8);

the Approved Product contains a Contracting Wheel and Index Wheel positioned in order to engage the Coiled Strip and peel its two Sheets apart during operation of the Inhalation Device so as to open each Pocket containing the Drug Substance, (See EXHIBIT 5, Figures E6 & E8);

the Approved Product contains a Drug Exit Port which is aligned with an open Pocket of Drug Substance and a Mouth Piece through which a user can inhale the Drug Substance in powder form, (See EXHIBIT 5, Figures E6 & E8);

the Approved Product contains an Index Wheel, Contracting Wheel and Base Wheel,

along with a Contracting Wheel Column, Index Ratchet, Contracting Wheel Ratchet Gear, Idler Gear and Lever for indexing or positioning the opened Pockets in line with the Drug Exit Port (See EXHIBIT 5, Figures E6 & E8).

(b) Claim 2 reads as follows:

A device according to claim 1, adapted for use where one of such peelable sheets is a base sheet having a plurality of pockets therein, and

an other of such peelable sheets is a lid sheet, each pocket and an adjacent part of such a lid sheet defining a respective one of such containers, said means positioned to engage comprising driving means for pulling such a lid sheet and a base sheet apart at the opening station.

Claim 2 reads on the Approved Product being that:

the Approved Product contains a Coiled Strip having two sheets that may be peeled apart during operation of the device, one being a Base Strip which contains the recessed portion of the Pocket and creates an "open pocket", the other sheet being a Lid Strip which when secured to the Base Strip closes the open Pocket; (See EXHIBIT 5, Figures E6 & E8).

the Approved Product contains an Index Wheel, Contracting Wheel and Base Wheel, along with a Contracting Wheel Column, Index Ratchet, Contracting Wheel Ratchet Gear, Idler Gear, Lever and a Manifold for peeling apart the Base Strip and the Lid Strip and indexing (or positioning) the opened Pockets in line with the Drug Exit Port (See EXHIBIT 5, Figures E6 & E8).

(c) Claim 3 reads as follows:

A device according to claim 2, comprising indexing means engageable between adjacent pockets to cause each pocket in turn to be positioned in communication with the outlet.

Claim 3 reads on the Approved Product being that:

the Approved Product contains an Index Wheel which has a plurality of grooves extending parallel to the axis of the wheel, wherein the grooves are spaced at a pitch which is equal to the distance between the center line of each of the Pockets in the Coiled Strip and wherein each groove will engage a pocket so as to cause movement of the Coiled Strip by one groove pitch upon operation to open a pocket and bring it into communication with the drug exit port. (See EXHIBIT 5, Figures E6 & E8)

(d) Claim 4 reads as follows:

A device according to claim 2, comprising at least one chamber for receiving medicament pack before opening, and for receiving the base sheet and lid sheet after peeling apart.

Claim 4 reads on the Approved Product being that:

the Approved Product contains three chambers formed by the Body Base, Manifold and Body Top, wherein a First Chamber houses the unopened Coiled Strip, a Second Chamber houses the peeled Lid Strip and a Third Chamber houses the peeled Base Strip. (See EXHIBIT 5, Figures E6 & E8)

(e) Claim 6 reads as follows:

A device according to claim 2, wherein the said driving means comprises lid driving means for pulling such a lid sheet.

Claim 6 reads on the Approved Product being that:

the Approved Product contains a Contracting Wheel which when actuated by the Lever together with the operation of the Index Wheel, Base Wheel, Contracting Wheel Column, Index Ratchet, Contracting Wheel Ratchet Gear and Idler Gear will pull the Lid Strip. (See EXHIBIT 5, Figures E6 & E8)

(f) Claim 9 reads as follows:

A device according to claim 6, comprising a rotatable index wheel having recesses therein, the wheel being engageable with such a medicament pack so that the recesses each receive a respective pocket.

Claim 9 reads on the Approved Product being that:

the Approved Product contains a rotatable Index Wheel which has a plurality of grooves extending parallel to the axis of the wheel, wherein the grooves are spaced at a pitch which is equal to the distance between the center line of each of the Pockets in the Coiled Strip and wherein each groove will engage each Pocket. (See EXHIBIT 5, Figures E6 & E8)

(g) Claim 10 reads as follows:

A device according to claim 9, wherein the index wheel and the lid driving means are interconnected so that the rotation of one correlates with the rotation of the other.

Claim 10 reads on the Approved Product being that:

the Approved Product contains the Index Wheel and the Contracting Wheel / Contracting Wheel Ratchet Gear, wherein the portion of the Index Wheel proximal to the Body Base is toothed, wherein the portion of the Contracting Wheel proximal to the Body Base is joined to a toothed Contracting Wheel Ratchet Gear and wherein the toothed portion of the Index Wheel and the Contracting Wheel Ratchet Gear interengage so that the rotation of one correlates with the rotation of the other. (See EXHIBIT 5, Figures E6 & E8)

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) necessary to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) Effective Date of IND

Applicant submitted an Investigational New Drug ("IND") application (43,097) for SEREVENT® DISKUS® on August 2, 1993. However, the product used in the clinical trials described in the approved package insert for SEREVENT® DISKUS® was tested under IND 35,239 for salmeterol xinafoate powder delivered by the Rotadisk®/Diskhaler® System. IND 35,239 was submitted on August 6, 1990. Therefore, Applicant submits that IND 35,239 controls for purposes of determining the applicable regulatory review period for extending U.S. 5,590,645.

The "effective date" of IND 35,239 however is unclear from the record. The record indicates that Applicant submitted the IND to the FDA on August 6, 1990. On August 14, FDA informed Applicant that clinical trials should not proceed until September 7, 1990 (30 days after FDA received IND 35,239) unless FDA informed it otherwise. On September 10, 1990, the FDA informed Applicant that the compound was safe to administer to humans but requested that clinical trials be deferred until questions concerning the study design were answered. On February 22, 1991, FDA notified Applicant that the study could proceed. It is unclear whether IND 35,239 was placed on "clinical hold" pursuant to 21 C.F.R. § 312.42 or merely "commented on" pursuant to §312.41. If the former is the case, then the "effective date" for purposes of determining the regulatory review period would be the date the "clinical hold" is removed or February 22, 1991. If the latter is the case, the "effective date" would be either 30 days after the FDA received the IND (September 7, 1990) or the date the FDA indicated that the compound was "safe" (September 10, 1990). Therefore, Applicant respectfully submits that the effective date for IND 35,239 is September 7, 1990, in the alternative September 10, 1990 and in the third alternative February 22, 1991. Applicant further submits that regardless of which of the above three dates is found to be correct, the length of the extension sought herein will not be affected since U.S. 5,590,645 issued during the NDA period. See EXHIBITS 8 and 9.

(b) Issue Date of Patent

U.S. Patent No. 5,590,645 issued January 7, 1997 and claims a product under section 156(f). See EXHIBITS 4 and 5.

(c) Submission Date of NDA

Applicant submitted a New Drug Application (NDA 20-692) for SEREVENT® DISKUS® on June 18, 1996. See EXHIBIT 10.

(d) Approval Date of NDA

NDA 20-692 for SEREVENT® DISKUS® was approved by the FDA on September 19, 1997. See EXHIBIT 3.

(11) A brief description of each significant activity undertaken by Applicant during both the IND and NDA regulatory periods is presented in chronological form and is attached hereto as EXHIBITS 8 and 9, "Document Chronologies / Due Diligence Logs".

(a) The Due Diligence Log reflects significant communications between Applicant and FDA during regulatory periods. Such communications may include, but are not limited to: submission of pre-clinical reports; registration of clinical protocols and amendments thereof; registration of clinical investigators and amendments thereof; submission of adverse event reports; submission of IND Annual Reports, etc.

(b) Periods between such communications enumerated in the Due Diligence Log reflect Applicant's diligent undertaking of the necessary clinical studies and other activities required by the FDA in order to obtain approval for Applicant's product.

(12) Applicant is of the opinion that U.S. Patent 5,590,645 is eligible for a 246-day extension subject to the 14 year limitation pursuant to 35 U.S.C. § 156(c)(3).

(a) Applicant has satisfied the eligibility criteria necessary to obtain a patent term extension pursuant to 35 U.S.C. § 156.

(1) 35 U.S.C. § 156(a)
U.S. Patent 5,590,645 claims a "product" pursuant to section 156(f).

(2) 35 U.S.C. § 156(a)(1)
The term of U.S. Patent 5,590,645 has not expired before submission of this application.

(3) 35 U.S.C. § 156(a)(2)
The term of U.S. Patent 5,590,645 has never been extended.

(4) 35 U.S.C. § 156(a)(3)
The application for extension is submitted by the owner of record in accordance with the requirements of 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.*

(5) 35 U.S.C. § 156(a)(4)
The Approved Product, SEREVENT® DISKUS®, has been subject to a regulatory review period before its commercial marketing or use.

(6) 35 U.S.C. § 156(a)(5)(A)
The commercial marketing or use of the Approved Product, SEREVENT® DISKUS®, after the regulatory review period is the first permitted commercial marketing or use of the Approved Product under the provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) under which such regulatory review period occurred.

(b) Applicant herewith, claims a patent term extension of 246 days for U.S. Patent 5,590,645 pursuant to 35 U.S.C. § 156(g) and subject to the limitation of 35 U.S.C. §156(c)(3) as follows:

(1) One-half of the IND regulatory review period for the Approved Product beginning February 22, 1991 and ending on June 17, 1996 (one day prior to the date on which the NDA for the Approved Product was submitted) such period being equal to 1055 days. See EXHIBIT 7.

(2) The full term of the NDA regulatory review period commencing June 18, 1996 (the date NDA 20-692 for the Approved Product was submitted) and ending on September 19, 1997 (the date on which NDA 20-692 was approved), such period being equal to 459 days. See EXHIBIT 7.

(3) The sum of one-half the IND period and the NDA period equals 1514 days.

(c) Applicant herewith, claims an expiration date of September 19, 2011 for U.S. Patent 5,590,645 pursuant to 35 U.S.C. § 156(c)(3).

(1) The expiration of U.S. Patent 5,590,645, 20 years from its first U.S. filing date is March 1, 2011 pursuant to the Uruguay Round Agreements Act, Public Law 103-465 (1994).

(2) Extending the March 1, 2011 expiration by 246 days would result in an expiration date of November 2, 2011.

(3) Being that 35 U.S.C. § 156(c)(3) requires that term extensions, if necessary, be reduced in order to limit the expiration date of a patent receiving term extensions to 14 years after the date of NDA approval, the expiration date of U.S. Patent 5,590,645 is limited to September 19, 2011. See EXHIBIT 7.

(13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension.

(14) The Commissioner of Patents and Trademarks is authorized to charge deposit account 07-1392 in the amount of $1,060.00 for receiving and acting upon this application for extension of term. In the event the actual fee differs from that specified above, it is requested that the overpayment be charged or the underpayment credited as authorized in the letter by the Undersigned enclosed herewith.

(15) Inquiries and correspondence relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.

Patent Counsel

Glaxo Wellcome Inc.

Five Moore Drive

Research Triangle Park, NC 27709

(919) 483-7656

(16) A duplicate of the application papers, certified as such is attached hereto.

(17) Submitted herewith is a Declaration by Shah R. Makujina, Patent Attorney for Glaxo Wellcome Inc., which meets the criteria set forth in 37 C.F.R. § 1.740(b).

The undersigned hereby certifies that this Application for Extension of Patent Term under 35 U.S.C. § 156 is being submitted as duplicate originals and three copies and its EXHIBITS and supporting papers as five copies.

Respectfully submitted,

By: Glaxo Wellcome Inc.

November 7, 1997
Date

Shah R. Makujina
Reg. No. 41,174
Attorney for Applicant

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Phone: (919) 483-1276
Facsimile: (919) 483-7988

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re	:	U.S. Patent No. 5,590,645
Issued	:	January 7, 1997
Inventors	:	Michael B. Davies, David J. Hearne, Paul K. Rand and Richard I. Walker
Assignee	:	Glaxo Group Limited
For	:	INHALATION DEVICE

Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

Sir:

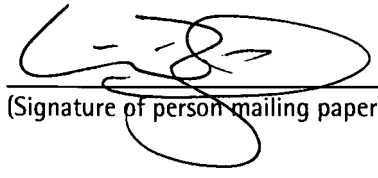
Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM under 35 U.S.C. §156 with regard to U.S. Patent No. 5,590,645.

The Commissioner is hereby authorized to charge Deposit Account No. 07-1392 in the amount of $1,060.00 to cover the application fee. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit overpayment to Account No. 07-1392 . Duplicate copies of this letter are enclosed.

CERTIFICATION UNDER 37 C.F.R. § 1.10

I hereby certify that this Application for Extension of Patent Term and the documents referred to therein are being deposited with the United States Postal Service on this date November 7, 1997 in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EM 484296056US addressed to the: Commissioner of Patents and Trademarks, Box Patent Ext., Washington, D.C. 20231.

Shah R. Makwana
(Type or print name of person mailing paper)



(Signature of person mailing paper)

Please address all communications relating to the enclosed APPLICATION FOR EXTENSION OF PATENT TERM to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
Telephone No. (919) 483-7656

Respectfully submitted,
By: Glaxo Wellcome Inc.

November 7, 1997
Date

Shah R. Makujina
Reg. No. 41,174
Attorney for Applicant

Glaxo Wellcome Inc.
Five Moore Drive
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Phone: (919) 483-1276
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Issued	:	January 7, 1997
Inventors	:	Michael B. Davies, David J. Hearne, Paul K. Rand and Richard I. Walker
Assignee	:	Glaxo Group Limited
For	:	INHALATION DEVICE

Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

Declaration Under 37 C.F.R. § 1.740(b)

To the Commissioner of Patents and Trademarks:

I, Shah R. Makujina, residing in Durham, North Carolina, declare as follows:

(1) That I am a patent attorney authorized to practice before the United States Patent and Trademark Office and that my registration number is 41,174.

(2) That I make this declaration as a Patent Attorney for Glaxo Wellcome Inc., a corporation of the State of North Carolina having a place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709 and have general authority to act on its behalf in patent matters.

(3) That Glaxo Group Limited is the assignee of the entire right, title and interest in United States Patent 5,590,645 issued January 7, 1997 (hereinafter "Patent") and has authorized Glaxo Wellcome Inc. pursuant to the attached Power of Attorney to file the instant Application for Extension of Patent Term. See Exhibit 1.

(4) That I have general authority in patent matters to act on behalf of Glaxo Group Limited pursuant to the attached Power of Attorney.

(5) That I have reviewed and understand the contents of the Application for Extension of Patent Term submitted herewith on behalf of Glaxo Wellcome Inc. requesting a 246-day extension of the term of the Patent, to be limited only by the 14-year cap under 35 U.S.C. § 156(c)(3), is justified under 35 U.S.C. § 156 and applicable regulations.

(6) That I believe that the Patent is subject to extension pursuant to 37 C.F.R. § 1.710.

(7) That I believe that a 246-day extension of the term of the Patent, to be limited only by the 14-year limitation under 35 U.S.C. § 156(c)(3), is justified under 35 U.S.C. § 156 and applicable regulations.

(8) That I believe the Patent meets the conditions for the extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 5,590,645 and any extensions thereof.

Respectfully submitted,

November 7, 1997
Date

Shah R. Makujina
Reg. No. 41,174
Attorney for Applicant

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Phone: (919) 483-1276
Facsimile: (919) 483-7988

EXHIBIT 1

Declaration and Power of Attorney
37 C.F.R. 3.73(b)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent No. 5,590,645
Issued	:	January 7, 1997
Inventors	:	Michael B. Davies, David J. Hearne, Paul K. Rand and Richard I. Walker
Assignee	:	Glaxo Group Limited
For	:	INHALATION DEVICE

Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

Declaration and Power of Attorney

37 C.F.R. § 3.73(b)

To the Commissioner of Patents and Trademarks:

I, Graham George Brereton, declare as follows:

(1) That I am an Attorney of Glaxo Group Limited, a company incorporated in England and having its registered address at Glaxo Wellcome House, Berkeley Avenue, Greenford, United Kingdom, UB6 ONN, by virtue of a Power of Attorney granted by Glaxo Group Limited which empowers me to act on behalf of Glaxo Group Limited.

(2) That pursuant to 37 C.F.R. § 3.73(b) and 35 U.S.C. § 156(d)(1) , Glaxo Group Limited is the record owner and assignee of the entire interest in and to U.S. Patent No. 5,590,645 recorded in the United States Patent and Trademark Office on March 15, 1991, Reel 5645, Frame 0202.

(3) That I have reviewed the evidentiary documents for the aforesaid chain of title and hereby certify pursuant to 37 C.F.R. § 3.73(b) that, to the best of my knowledge and belief, title is in the assignee, Glaxo Group Limited by virtue of the above noted assignment.

(4) That Glaxo Group Limited does hereby make, constitute and appoint Glaxo Wellcome Inc. organized under the laws of North Carolina, having their principal place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709, United States of America as its special, true and lawful agent and attorney for the limited purpose of preparing and filing with the U.S. Patent and Trademark office an Application for Extension of Patent Term pursuant to 35 U.S.C. § 156 in respect of U.S. Patent No. 5,590,645 which Patent is owned by Glaxo Group Limited, and prosecuting said Application; and to do and perform each and every act in

connection with the above stated purpose which Glaxo Wellcome Inc. deems necessary or desirable.

(5) That Glaxo Group Limited herein issues general authority to the following attorney(s) and/or agent(s), each of Glaxo Wellcome Inc., to prosecute this Application and transact all business in the Patent and Trademark Office connected therewith.

David J. Levy	Reg. No. 27,655	James P. Riek	Reg. No. 39,009
Shah R. Makujina	Reg. No. 41,174	Charles E. Dadswell	Reg. No. 35,851
Robert T. Hrubiec	Reg. No. 36,392	Robert H. Brink	Reg. No. 36,094
Frank P. Grassler	Reg. No. 31,164	LaVonda R. DeWitt	Reg. No. 40,396
Karen L. Prus	Reg. No. 39,337		

(6) That any inquiries and correspondence relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

The undersigned further declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 5,590,645 and any extensions thereof.

Glaxo Group Limited,

November 1, 1997
Date

By: Graham George Brereton
Attorney for Glaxo Group Limited

EXHIBIT 2

Assignment of
Application for Letters Patent of the United States

No. 663,145 abandoned in favor of continuation application
No. 175,174 abandoned in favor of continuation application
No. 552,166 which issued as

U.S. Patent 5,590,645

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: DARBY & DARBY
805 THIRD AVENUE
NEW YORK, NY 10022

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 DAVIES, MICHAEL B.	DOC DATE: 02/15/91
ASSIGNOR: 002 HEARNE, DAVID J.	DOC DATE: 02/15/91
ASSIGNOR: 003 RAND, PAUL K.	DOC DATE: 02/15/91
ASSIGNOR: 004 WALKER, RICHARD I.	DOC DATE: 02/15/91

RECORDATION DATE: 03/15/91 NUMBER OF PAGES 004 REEL/FRAME 5645/0202

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 GLAXO GROUP LIMITED, CLARGES HOUSE, 6/12 CLARGES ST., LONDON W1Y 8DH, ENGLAND

SERIAL NUMBER	7-663145	FILING DATE	03/01/91
PATENT NUMBER		ISSUE DATE	00/00/00

8.00-518 HLD

CERTIFICATE OF MAILING

I hereby certify that this paper and every paper referred to therein as being enclosed herewith is being deposited with the U.S. Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner of Patents & Trademarks, Washington, DC 20231, on MARCH 13, 1991 (Date of Deposit)

3/13/91 Donna Greenberg
Date Name

File No: 2954/06403

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MICHAEL BIRSHA DAVIES, DAVID JOHN HEARNE, PAUL KENNETH RAND and RICHARD IAN WALKER

Serial No: 663,145 Group Art Unit:

Filed: 1 March 1991 Examiner:

For: INHALATION DEVICE

RECEIVED
MAR 22 1991
PATENT APPLICATION DIVISION

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

RECORDED: 03/26/1991 FRAME: 202

COMPLETION OF PATENT APPLICATION

This following items are submitted herewith in completion of the above-identified patent application:

1. [X] Declaration, petition and power of attorney (with copy of specification)

2. [X] Check in the amount of $878.00, (X filing; X recording) (See attached Fee Computation Sheet)

3. [X] Informal drawings, 28 sheets (Figs. 1-35) 93182860

4. [X] Assignment for recording to: GLAXO GROUP LIMITED

Priority is claimed for this application, corresponding application/s having been filed as follows:

Country : United Kingdom
Number : 90 04781.2
Date : 2 March 1990

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ASSIGNMENT BRANCH

The priority documents [X] are enclosed

The Patent Office is authorized to charge any deficiency up to $300.00 in the above fees, and to credit any excess, to our Deposit Account No. 4-0100.

Respectfully submitted,

Dated: 13 March 1991

Paul Fields
Reg. No. 20,298
Attorney for Applicant(s)

DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022
212-527-7700

File No: 2954/06403

PATENT FEE COMPUTATION SHEET

	No. of Claims Presented		Extra Claims Previously Paid For		Number of Extra Claims		Rate		
Basic Fee									$630.00
Total Claims	26	-20 -	0	=	6	x	$20	=	$120.00
Independent Claims:	2	- 3 -	0	=	0	x	$60	=	$ -0-
Multiple Dependent Claims Presented:	If so, add						$120	=	$ -0-
TOTAL FILING FEE									$750.00

Surcharge for late submission of filing fee and/or declaration ($120)	$120.00
SUBTOTAL	$870.00
[ ] Small Entity REDUCTION (Half of Subtotal)	$ -0-
Fee for recordation of assignment ($8.00)	$ 8.00
Charge for filing application non-English Language ($30.00)	$ -0-
TOTAL	$878.00

EXHIBIT 3

FDA Approval Letter for

SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) for Oral Inhalation Only

NDA 20-692

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-692

SEP 19 1997

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, North Carolina 27709

Attention: John W. Morgan, Ph.D.
Director, Regulatory Affairs

Dear Dr. Morgan:

Please refer to your pending new drug application dated June 18, 1996, received June 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serevent® Diskus® (salmeterol xinafoate inhalation powder).

We acknowledge receipt of your submissions dated June 26, September 20, 23, and 27, October 8, 16, and 21, November 19, 20, and 21, 1996, and January 28, April 1, 17, 21, and 23, May 30, June 18, July 22, and 25, August 22, 24, and 26, and September 15, 16, and 18, 1997. Your submission dated May 30, 1997, extended the user fee due date to September 19, 1997.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting beta$_2$-agonists, as recommended in the draft physician labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the mock-up carton and container labels submitted on September 18, 1997, and the enclosed marked-up draft physician labeling and patient package insert. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or

similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-692." Approval of this submission by FDA is not required before the FPL may be used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated May 30, August 24, and September 15, 1997. These commitments are listed below.

1. The following commitments pertain to the Lactose Monohydrate NF.

   a. As stated in your August 24, 1997, submission, a numerical specification value for the amorphous content of lactose monohydrate used in this drug product will be submitted by January 2, 1998, as a supplement. Please note that this value should be consistent with your currently proposed specification of "no detectable amorphous content" and the LOD of the analytical method used.

   b. A test and specification for lactose monohydrate assay to be performed as part of your reduced incoming inspection program for the lactose monohydrate NF used in this drug product, will be submitted by January 2, 1998, as a supplement. The specifications will be based on and reflective of the data; and the data will be obtained from samples of similar or higher quality as compared to the lactose monohydrate used to make the clinical supplies.

   c. As stated in your August 24, 1997, submission, the following tests will be performed:

      (1) Particle size and amorphous content testing on every batch of lactose monohydrate in addition to identification and microbial testing on every batch and full testing on every tenth batch; and

      (2) revert to full testing for every batch of lactose monohydrate if any batch fails to comply with any specification, until 3 consecutive batches comply with all specifications.

d. An updated specification sheet, monographs, and other relevant documents for the lactose monohydrate NF to be used in this drug product which reflects all of the agreements and commitments as described in your August 24, 1997, submission, in this letter and in previous letters and submissions associated with this NDA will be submitted as a supplement by January 2, 1998. The supplement should include your most recent tests and specifications for total organic volatile impurities (OVI) content, particle shape and morphology, and pH (include the numerical value of the concentration used for the test solution).

2. We acknowledge your initial and 3-month stability results from the ongoing studies of unwrapped drug product stored at 25°C/75%RH. The data for drug hold-up in the mouthpiece and manifold areas (as one group), for the initial and 3-month samples (if available) and for the upcoming 6-month testing time point for the 3 batches being evaluated will be submitted by January 2, 1998, as a supplement.

3. As stated in your September 15, 1997, submission, a further data-based verification of the eight (8) week patient-use-expiry period from the first three post-approval commercial batches will be submitted by January 31, 1998. We remind you that if the eight week patient-use-expiry period is not supportable at that time, you commit to immediately take action to appropriately shorten this expiry period by submission of a supplement.

4. As stated in your May 30, 1997, submission, a final report for the study cited on page 77 will be submitted by September 30, 1997. We note that the results of this study (30°C/75%RH, sequential testing of devices through life) appear to contradict the results of your related study being conducted at 25°C/75%RH (6-month testing time point pending). Therefore, a one-time study for emitted dose and PSD by CI with at least monthly testing of unwrapped drug product stored at 30°C/75%RH over a 6-month test interval will be conducted and data submitted by May 31, 1998.

5. Validation information for the revised method for manifold extractables will be submitted by January 2, 1998, as a supplement. A proposal to update the methods will be submitted by the fourth quarter of 1998.

6. Foreign particulate matter in the drug product in the LT 100 micron and LT 10 micron size ranges with regard to the number of particles and type of material (i.e., plastic, metal, etc.) in those size ranges will be characterized and appropriate test methods and specifications for these size ranges will be proposed within 6 months of the date of this letter as a supplement.

7. As stated in your August 24, 1997, submission, alternative methods for particle size distribution analysis which will allow for a quantitative evaluation of a greater portion of the emitted dose as listed on page 23 will be investigated. Data will be submitted every 6 months beginning February 1998.

In addition, we remind you of the following agreements.

8. You have agreed to an 18-month expiration dating period for this product until sufficient stability data are available (i.e., from a minimum of the first 3 post-approval commercial batches, with appropriate statistical treatment) to support a new proposal for the expiration dating period.

9. Updated master batch records which reflect all changes and updates will be submitted within one month after the approval of the NDA.

10. Provide available methods validation package as soon as possible and the final update, which will include all updated documentation for monographs, specification sheets, etc. by January 2, 1998.

Protocols, data, and final reports related to the Phase 4 commitments should be submitted to this NDA. For administrative purposes, all submissions, including all supplements, relating to these Phase 4 commitments must be clearly designated as "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug product when it is available.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Parinda Jani
Project Manager
(301) 827-1057

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

EXHIBIT 4

Approved Product Information / Package Insert
for
SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) for Oral Inhalation Only

NDA 20-692

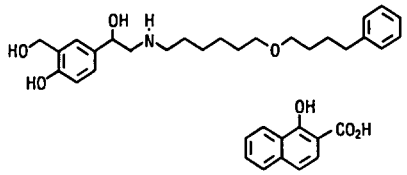
PRODUCT INFORMATION

SEREVENT®

(salmeterol xinafoate) Inhalation Aerosol

Bronchodilator Aerosol For Oral Inhalation Only

DESCRIPTION: SEREVENT Inhalation Aerosol contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective beta$_2$-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate has the following chemical structure:



The molecular weight of salmeterol xinafoate is 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. Salmeterol xinafoate is a white to off-white powder. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

SEREVENT Inhalation Aerosol is a pressurized, metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of salmeterol xinafoate in a mixture of two chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with lecithin. 36.25 mcg of salmeterol xinafoate is equivalent to 25 mcg of salmeterol base. Each actuation delivers 25 mcg of salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base (as salmeterol xinafoate) from the actuator.

CLINICAL PHARMACOLOGY:

Mechanism of Action: Salmeterol is a long-acting beta-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta$_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta$_1$- and beta$_2$-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta$_2$-adrenoceptors than albuterol. Although beta$_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-adrenoceptors are the predominant receptors in the heart, there are also beta$_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these is not yet established, but they raise the possibility that even highly selective beta$_2$-agonists may have cardiac effects.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, salmeterol inhibits both the early- and late-phase responses to inhaled allergens, the latter persisting for over 30 hours after a single dose when the bronchodilator effect is no longer evident. Single doses of salmeterol also attenuate allergen-induced bronchial hyper-responsiveness.

Pharmacokinetics: Salmeterol acts locally in the lung; plasma levels therefore do not predict therapeutic effect. Because of the low therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (42 mcg twice daily). Following chronic administration of an inhaled dose of 42 mcg twice daily, salmeterol was detected in plasma within 5 to 10 minutes in six asthmatic patients; plasma concentrations were very low, with peak concentrations of 150 pg/mL and no accumulation with repeated doses. Larger inhaled doses gave approximately proportionally increased blood levels. In these patients, a second peak

concentration of 115 pg/mL occurred at about 45 minutes, probably due to absorption of the swallowed portion of the dose (most of the dose delivered by a metered-dose inhaler is swallowed). Oral administration of 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) to two healthy subjects gave peak plasma salmeterol concentrations of about 650 pg/mL at about 45 minutes; the terminal elimination half-life was about 5.5 hours (one volunteer only).

Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and excreted independently. Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. In the two subjects discussed above, approximately 25% and 60% of orally administered radioactivity was eliminated in urine and feces, respectively, over a period of 7 days. No significant amount of unchanged salmeterol base was detected in either urine or feces.

Salmeterol is 94% to 98% bound to human plasma proteins in vitro over the concentration range of 8 to 7,722 ng of base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

The xinafoate moiety has no apparent pharmacologic activity, is highly protein bound (>99%), and has a long elimination half-life of 11 days.

The pharmacokinetics of salmeterol base have not been studied in elderly patients nor in patients with hepatic or renal impairment. Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Pharmacodynamics and Clinical Trials: Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some patients produce cardiovascular effects (see PRECAUTIONS). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol administration occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg resulted in heart rate increases of 3 to16 beats/min, about the same as albuterol (4 to 10 beats/min). In two double-blind studies, patients receiving either salmeterol (n = 81) or albuterol (n = 80) underwent continuous electrocardiographic monitoring during four 24-hour periods; no clinically significant dysrhythmias were noted.

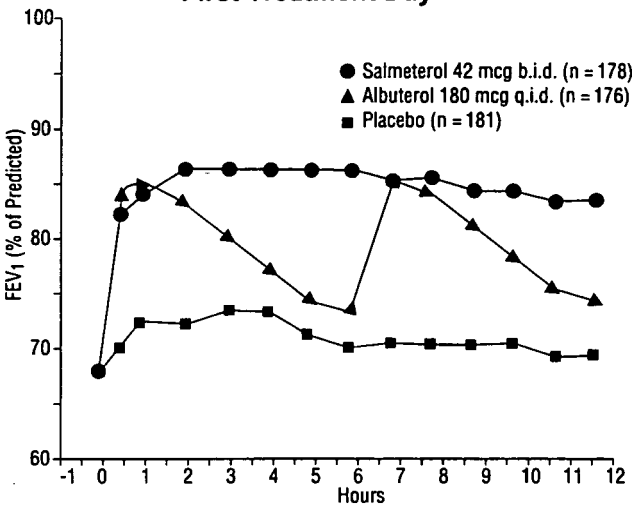
Beta-agonists and methylxanthines administered concurrently in laboratory animals (minipigs, rodents, and dogs) cause cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis). Whether these findings are relevant to humans is not known.

In placebo- and albuterol-controlled, single-dose clinical trials with SEREVENT Inhalation Aerosol, the time to onset of effective bronchodilatation (>15% improvement in forced expiratory volume in 1 second [FEV_1]) was 10 to 20 minutes after a 42-mcg dose. Maximum improvement in FEV_1 generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

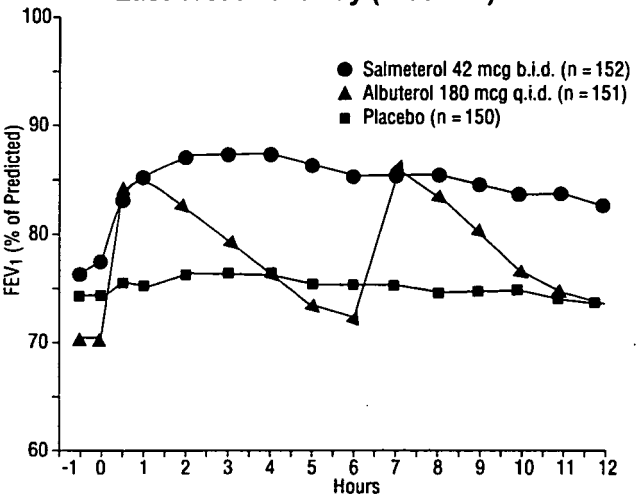
In two large, randomized, double-blind studies, SEREVENT Inhalation Aerosol was compared with albuterol and placebo in patients with mild-to-moderate asthma, including both patients who did and who did not receive concomitant inhaled corticosteroids. The efficacy of SEREVENT Inhalation Aerosol was demonstrated over the 12-week period with no change in effectiveness over this period of time. There were no gender-related differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect has been noted in these studies. FEV_1 measurements (percent of predicted) from these two 12-week trials are shown below for both the first and last treatment days.

FEV_1, as Percent of Predicted, From Two Large 12-Week Clinical Trials

First Treatment Day



Last Treatment Day (Week 12)



During daily treatment with SEREVENT Inhalation Aerosol for 12 weeks in patients with asthma, the following treatment effects were seen:

Daily Efficacy Measurements In Two Large 12-Week Clinical Trials (Combined Data)

Parameter	Time	Placebo	SEREVENT	Albuterol
No. of randomized subjects		187	184	185
Mean AM PEFR (L/min)	baseline	412	409	398
	12 weeks	414	438*	390
Mean % days with no symptoms	baseline	11	11	14
	12 weeks	17	35*	24
Mean % nights with no awakenings	baseline	67	67	65
	12 weeks	74	87*	74
Rescue medications (mean no. of inhalations per day)	baseline	4.4	4.1	4.0
	12 weeks	3.3	1.3†‡	1.9
Relative proportion of total no. asthma exacerbations		55%	17%	28%

*$P<0.001$ versus albuterol and placebo
†$P<0.05$ versus albuterol
‡$P<0.001$ versus placebo

Safe usage with maintenance of efficacy for periods up to 1 year has been documented.

Protection against exercise-induced bronchospasm was examined in three controlled studies. Based on median values, patients who received SEREVENT Inhalation Aerosol had consistently less exercise-induced fall in FEV_1 than patients who received placebo, and they were protected for a longer period of time than patients who received albuterol (see table below). There were, however, some patients who were not protected from exercise-induced bronchospasm after SEREVENT administration and others in whom protection against exercise-induced bronchospasm decreased with continued administration over a period of 4 weeks.

Exercise-Induced Bronchospasm
Mean Percentage Fall in Postexercise FEV_1

Clinical Trials/ Time After Dose	Treatment		
	Placebo	SEREVENT	Albuterol
Study A: 1st Dose			
6 hours	37	9*	
12 hours	27	16*	
Study A: 4th Week			
6 hours	30	19	
12 hours	24	12	
Study B:			
1 hour	37	0*	2*
6 hours	37	5*†	27
12 hours	34	6*†	33
Study C:			
0.5 hour	43	16*	8*
2.5 hours	33	12*†	30
4.5 hours	—	12†	36
6.0 hours	—	19†	41

* Statistically superior to placebo ($P \leq 0.05$).
† Statistically superior to albuterol ($P \leq 0.05$).

INDICATIONS AND USAGE: SEREVENT Inhalation Aerosol is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting $beta_2$-agonists. It should not be used in patients whose asthma can be managed by occasional use of short-acting, inhaled $beta_2$-agonists.

SEREVENT Inhalation Aerosol may be used with or without concurrent inhaled or systemic corticosteroid therapy.

SEREVENT Inhalation Aerosol is also indicated for prevention of exercise-induced bronchospasm in patients 12 years of age and older.

CONTRAINDICATIONS: SEREVENT Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to any of the components.

WARNINGS:
IMPORTANT INFORMATION: SEREVENT INHALATION AEROSOL SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported, both in the United States and worldwide, when SEREVENT Inhalation Aerosol has been initiated in this situation.

Although it is not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT Inhalation Aerosol in this setting is inappropriate.

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe a short-acting, inhaled $beta_2$-agonist for this purpose as well as warn them that increasing inhaled $beta_2$-agonist use is a signal of deteriorating asthma.

SEREVENT INHALATION AEROSOL IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when SEREVENT Inhalation Aerosol is initiated.

(See PRECAUTIONS: Information for Patients and PATIENT'S INSTRUCTIONS FOR USE.)

1. Do Not Introduce SEREVENT Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma: SEREVENT Inhalation Aerosol is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that SEREVENT Inhalation Aerosol provides greater efficacy than or additional efficacy to short-acting, inhaled $beta_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported, both in the United States and worldwide, in patients receiving SEREVENT Inhalation Aerosol. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting $beta_2$-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT Inhalation Aerosol

contributed to these events or simply failed to relieve the deteriorating asthma.

2. Do Not Use SEREVENT Inhalation Aerosol to Treat Acute Symptoms: A short-acting, inhaled $beta_2$-agonist, not SEREVENT Inhalation Aerosol, should be used to relieve acute asthma symptoms. When prescribing SEREVENT Inhalation Aerosol, the physician must also provide the patient with a short-acting, inhaled $beta_2$-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice daily (morning and evening) use of SEREVENT Inhalation Aerosol.

When beginning treatment with SEREVENT Inhalation Aerosol, patients who have been taking short-acting, inhaled $beta_2$-agonists on a regular basis (e.g., q.i.d.) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute asthma symptoms while taking SEREVENT Inhalation Aerosol (see PRECAUTIONS: Information for Patients).

3. Watch for Increasing Use of Short-Acting, Inhaled $Beta_2$-Agonists, Which Is a Marker of Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's short-acting, inhaled $beta_2$-agonist becomes less effective or the patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses four or more inhalations per day of a short-acting, inhaled $beta_2$-agonist for 2 or more consecutive days, or if more than one canister (200 inhalations per canister) of short-acting, inhaled $beta_2$-agonist is used in an 8-week period in conjunction with SEREVENT Inhalation Aerosol, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT Inhalation Aerosol in this situation is not appropriate. SEREVENT Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose of two inhalations.**

4. Do Not Use SEREVENT Inhalation Aerosol as a Substitute for Oral or Inhaled Corticosteroids: There are no data demonstrating that SEREVENT Inhalation Aerosol has a clinical anti-inflammatory effect and could be expected to take the place of, or reduce the dose of, corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating SEREVENT Inhalation Aerosol. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

5. Do Not Exceed Recommended Dosage: As with other inhaled $beta_2$-adrenergic drugs, SEREVENT Inhalation Aerosol should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT_c interval, which has the potential for producing ventricular arrhythmias.

6. Paradoxical Bronchospasm: As with other inhaled asthma medications, paradoxical bronchospasm (which can be life threatening) has been reported following the use of SEREVENT Inhalation Aerosol. If it occurs, treatment with SEREVENT Inhalation Aerosol should be discontinued immediately and alternative therapy instituted.

7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of SEREVENT Inhalation Aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, and bronchospasm.

8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving SEREVENT Inhalation Aerosol.

PRECAUTIONS:

General: 1. Use With Spacer or Other Devices: The safety and effectiveness of SEREVENT Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

2. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of SEREVENT Inhalation Aerosol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency,

cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

3. Metabolic Effects: Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. No effects on glucose have been seen with SEREVENT Inhalation Aerosol at recommended doses. Administration of $beta_2$-adrenoceptor agonists may cause a decrease in serum potassium, possibly through intracellular shunting, which has the potential to increase the likelihood of arrhythmias. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT Inhalation Aerosol at recommended doses.

Information for Patients: See illustrated Patient's Instructions for Use. **SHAKE WELL BEFORE USING.**

It is important that patients understand how to use SEREVENT Inhalation Aerosol appropriately and how it should be used in relation to other asthma medications they are taking. Patients should be given the following information:

1. Shake well before using.
2. The recommended dosage (two inhalations twice daily, morning and evening) should not be exceeded.
3. SEREVENT Inhalation Aerosol is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with a short-acting, inhaled $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).
4. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma.
   - Decreasing effectiveness of short-acting, inhaled $beta_2$-agonists
   - Need for more inhalations than usual of short-acting, inhaled $beta_2$-agonists
   - Use of four or more inhalations per day of a short-acting $beta_2$-agonist for 2 or more days consecutively
   - Use of more than one canister of a short-acting, inhaled $beta_2$-agonist in an 8-week period (i.e., canister with 200 inhalations)
5. SEREVENT Inhalation Aerosol should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT Inhalation Aerosol.
6. Patients should be cautioned regarding potential adverse cardiovascular effects, such as palpitations or chest pain, related to the use of additional $beta_2$-agonist.
7. In patients receiving SEREVENT Inhalation Aerosol, other inhaled medications should be used only as directed by the physician.
8. When using SEREVENT Inhalation Aerosol to prevent exercise-induced bronchospasm, patients should take the dose at least 30 to 60 minutes before exercise.

Drug Interactions: ***Short-Acting Beta-Agonists:*** In the two 3-month, repetitive-dose clinical trials (n = 184), the mean daily need for additional $beta_2$-agonist use was 1 to 1½ inhalations per day, but some patients used more. Eight percent of patients used at least eight inhalations per day at least on one occasion. Six percent used 9 to 12 inhalations at least once. There were 15 patients (8%) who averaged over four inhalations per day. Four of these used an average of 8 to 11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than eight inhalations per day of short-acting $beta_2$-agonists with SEREVENT Inhalation Aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving SEREVENT Inhalation Aerosol, nebulized albuterol (one dose in most) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of

salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of SEREVENT Inhalation Aerosol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving SEREVENT Inhalation Aerosol has not been completely evaluated. In one clinical trial, 87 patients receiving SEREVENT Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by SEREVENT Inhalation Aerosol therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, and leiomyomas of the uterus and a dose-related increase in the incidence of cysts in the ovaries. A higher incidence of leiomyosarcomas was not statistically significant; tumor findings were observed at oral doses of 1.4 and 10 mg/kg, which gave 9 and 63 times, respectively, the human exposure based on rodent:human AUC comparisons.

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/m^2]). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

No significant effects occurred in mice at 0.2 mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (15 times the recommended clinical dose on a mg/m^2 basis).

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg orally (about 160 times the recommended clinical dose on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** No significant effects of maternal exposure to oral salmeterol xinafoate occurred in the rat at doses up to the equivalent of about 160 times the recommended clinical dose on a mg/m^2 basis. Dutch rabbit fetuses exposed to salmeterol xinafoate in utero exhibited effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at 0.6 mg/kg given orally (12 times the recommended clinical dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10 mg/kg given orally (approximately 1,600 times the recommended clinical dose on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with SEREVENT Inhalation Aerosol in pregnant women. SEREVENT Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SEREVENT Inhalation Aerosol during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low (85 to 200 pg/mL) in humans. In lactating rats dosed with radiolabeled salmeterol, levels of radioactivity were similar in plasma and milk. In rats, concentrations of salmeterol in plasma and milk were similar. The xinafoate moiety is also transferred to milk in rats at concentrations of about half the corresponding level in plasma. However, since there is no experience with use of SEREVENT Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug,

taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SEREVENT Inhalation Aerosol in children younger than 12 years of age have not been established.

Geriatric Use: Of the total number of patients who received SEREVENT Inhalation Aerosol in all clinical studies, 241 were 65 years and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in four well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in two large parallel-group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the two latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

No apparent differences in the efficacy and safety of SEREVENT Inhalation Aerosol were observed when geriatric patients were compared with younger patients in clinical trials. As with other $beta_2$-agonists, however, special caution should be observed when using SEREVENT Inhalation Aerosol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

ADVERSE REACTIONS: Adverse reactions to salmeterol are similar in nature to reactions to other selective $beta_2$-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT Inhalation Aerosol in patients 12 years of age and older with asthma. The following table reports the incidence of adverse events in these two studies.

Adverse Experience Incidence in Two Large 12-Week Clinical Trials*

Adverse Event Type	Percent of Patients		
	Placebo n = 187	SEREVENT 42 mcg b.i.d. n = 184	Albuterol 180 mcg q.i.d. n = 185
Ear, nose, and throat			
Upper respiratory tract infection	13	14	16*
Nasopharyngitis	12	14	11
Disease of nasal cavity/sinus	4	6	1
Sinus headache	2	4	<1
Gastrointestinal			
Stomachache	0	4	0
Neurological			
Headache	23	28	27
Tremor	2	4	3
Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

*The only adverse experience classified as serious was one case of upper respiratory tract infection in a patient treated with albuterol.

The table above includes all events (whether considered drug related or nondrug related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the SEREVENT Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Cardiovascular: Tachycardia, palpitations.

Ear, Nose, and Throat: Rhinitis, laryngitis.

Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.

Hypersensitivity: Urticaria.

Mouth and Teeth: Dental pain.

Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.

Neurological: Nervousness, malaise/fatigue.

Respiratory: Tracheitis/bronchitis.

Skin: Rash/skin eruption.

Urogenital: Dysmenorrhea.

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose related.

Postmarketing Experience: In extensive US and worldwide postmarketing experience, serious exacerbations of asthma, including some that

have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS no. 1), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

Postmarketing experience includes rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking. Hypertension and arrhythmias have been reported.

OVERDOSAGE: Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QT_c interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

In these cases, therapy with SEREVENT Inhalation Aerosol and all beta-adrenergic–stimulant drugs should be stopped, supportive therapy provided, and judicious use of a beta-adrenergic blocking agent should be considered, bearing in mind the possibility that such agents can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

As with all sympathomimetic pressurized aerosol medications, cardiac arrest and even death may be associated with abuse of SEREVENT Inhalation Aerosol.

Rats and dogs survived the maximum practicable inhalation doses of salmeterol of 2.9 and 0.7 mg/kg, respectively. The maximum nonlethal oral doses in mice and rats were approximately 150 mg/kg and >1,000 mg/kg, respectively.

Dialysis is not appropriate treatment for overdosage of SEREVENT Inhalation Aerosol.

DOSAGE AND ADMINISTRATION: SEREVENT Inhalation Aerosol should be administered by the orally inhaled route only (see Patient's Instructions for Use). For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 12 years of age and older is two inhalations (42 mcg) twice daily (morning and evening, approximately 12 hours apart). Adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

To gain full therapeutic benefit, SEREVENT Inhalation Aerosol should be administered twice daily (morning and evening) in the treatment of reversible airway obstruction.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered. If symptoms arise in the period between doses, a short-acting, inhaled $beta_2$-agonist should be taken for immediate relief.

Prevention of Exercise-Induced Bronchospasm: Two inhalations at least 30 to 60 minutes before exercise have been shown to protect against exercise-induced bronchospasm in many patients for up to 12 hours. Additional doses of SEREVENT Inhalation Aerosol should not be used for 12 hours after the administration of this drug. Patients who are receiving SEREVENT Inhalation Aerosol twice daily (morning and evening) should not use additional SEREVENT Inhalation Aerosol for prevention of exercise-induced bronchospasm. If this dose is not effective, other appropriate therapy for exercise-induced bronchospasm should be considered.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with SEREVENT Inhalation Aerosol, efficacy and safety of 42 mcg given twice daily (morning and evening) did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

HOW SUPPLIED: SEREVENT Inhalation Aerosol is supplied in 13-g canisters containing 120 metered actuations in boxes of one. Each actuation delivers 25 mcg of salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base (as salmeterol xinafoate) from the actuator. Each canister is supplied with a green plastic actuator with a teal-colored strapcap and patient's instructions (NDC 0173-0464-00). Also available, SEREVENT Inhalation Aerosol

Refill (NDC 0173-0465-00), a 13-g canister only with patient's instructions.

SEREVENT Inhalation Aerosol is also supplied in a pack that consists of a 6.5-g canister containing 60 metered actuations in boxes of one. Each actuation delivers 25 mcg of salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base from the actuator (as salmeterol xinafoate). Each canister is supplied with a green plastic actuator with a teal-colored strapcap and patient's instructions (NDC 0173-0467-00).

For use with SEREVENT Inhalation Aerosol actuator only. The actuator should not be used with other aerosol medications.

Store between 15° and 30°C (59° and 86°F). Store canister with nozzle end down. Protect from freezing temperatures and direct sunlight.

Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperatures above 120°F. Keep out of reach of children. As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold; for best results, the canister should be at room temperature before use. Shake well before using.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

> **WARNING:** Contains trichlorofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the patient information leaflet of this product pursuant to EPA regulations.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

September 1996 RL-352

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re	:	U.S. Patent No. 5,590,645
Issued	:	January 7, 1997
Inventors	:	Michael B. Davies, David J. Hearne, Paul K. Rand and Richard I. Walker
Assignee	:	Glaxo Group Limited
For	:	INHALATION DEVICE

Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

Declaration Under 37 C.F.R. § 1.740(b)

To the Commissioner of Patents and Trademarks:

I, Shah R. Makujina, residing in Durham, North Carolina, declare as follows:

(1) That I am a patent attorney authorized to practice before the United States Patent and Trademark Office and that my registration number is 41,174.

(2) That I make this declaration as a Patent Attorney for Glaxo Wellcome Inc., a corporation of the State of North Carolina having a place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709 and have general authority to act on its behalf in patent matters.

(3) That Glaxo Group Limited is the assignee of the entire right, title and interest in United States Patent 5,590,645 issued January 7, 1997 (hereinafter "Patent") and has authorized Glaxo Wellcome Inc. pursuant to the attached Power of Attorney to file the instant Application for Extension of Patent Term. See Exhibit 1.

(4) That I have general authority in patent matters to act on behalf of Glaxo Group Limited pursuant to the attached Power of Attorney.

(5) That I have reviewed and understand the contents of the Application for Extension of Patent Term submitted herewith on behalf of Glaxo Wellcome Inc. requesting a 246-day extension of the term of the Patent, to be limited only by the 14-year cap under 35 U.S.C. § 156(c)(3), is justified under 35 U.S.C. § 156 and applicable regulations.

(6) That I believe that the Patent is subject to extension pursuant to 37 C.F.R. § 1.710.

(7) That I believe that a 246-day extension of the term of the Patent, to be limited only by the 14-year limitation under 35 U.S.C. § 156(c)(3), is justified under 35 U.S.C. § 156 and applicable regulations.

(8) That I believe the Patent meets the conditions for the extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 5,590,645 and any extensions thereof.

Respectfully submitted,

November 7, 1997
Date

Shah R. Makujina
Reg. No. 41,174
Attorney for Applicant

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Phone: (919) 483-1276
Facsimile: (919) 483-7988

EXHIBIT 1

Declaration and Power of Attorney
37 C.F.R. 3.73(b)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent No. 5,590,645
Issued	:	January 7, 1997
Inventors	:	Michael B. Davies, David J. Hearne, Paul K. Rand and Richard I. Walker
Assignee	:	Glaxo Group Limited
For	:	INHALATION DEVICE

Commissioner of Patent and Trademarks
Box Patent Ext.
Washington, DC 20231

Declaration and Power of Attorney

37 C.F.R. § 3.73(b)

To the Commissioner of Patents and Trademarks:

I, Graham George Brereton, declare as follows:

(1) That I am an Attorney of Glaxo Group Limited, a company incorporated in England and having its registered address at Glaxo Wellcome House, Berkeley Avenue, Greenford, United Kingdom, UB6 ONN, by virtue of a Power of Attorney granted by Glaxo Group Limited which empowers me to act on behalf of Glaxo Group Limited.

(2) That pursuant to 37 C.F.R. § 3.73(b) and 35 U.S.C. § 156(d)(1) , Glaxo Group Limited is the record owner and assignee of the entire interest in and to U.S. Patent No. 5,590,645 recorded in the United States Patent and Trademark Office on March 15, 1991, Reel 5645, Frame 0202.

(3) That I have reviewed the evidentiary documents for the aforesaid chain of title and hereby certify pursuant to 37 C.F.R. § 3.73(b) that, to the best of my knowledge and belief, title is in the assignee, Glaxo Group Limited by virtue of the above noted assignment.

(4) That Glaxo Group Limited does hereby make, constitute and appoint Glaxo Wellcome Inc. organized under the laws of North Carolina, having their principal place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709, United States of America as its special, true and lawful agent and attorney for the limited purpose of preparing and filing with the U.S. Patent and Trademark office an Application for Extension of Patent Term pursuant to 35 U.S.C. § 156 in respect of U.S. Patent No. 5,590,645 which Patent is owned by Glaxo Group Limited, and prosecuting said Application; and to do and perform each and every act in

connection with the above stated purpose which Glaxo Wellcome Inc. deems necessary or desirable.

(5) That Glaxo Group Limited herein issues general authority to the following attorney(s) and/or agent(s), each of Glaxo Wellcome Inc., to prosecute this Application and transact all business in the Patent and Trademark Office connected therewith.

David J. Levy	Reg. No. 27,655	James P. Riek	Reg. No. 39,009
Shah R. Makujina	Reg. No. 41,174	Charles E. Dadswell	Reg. No. 35,851
Robert T. Hrubiec	Reg. No. 36,392	Robert H. Brink	Reg. No. 36,094
Frank P. Grassler	Reg. No. 31,164	LaVonda R. DeWitt	Reg. No. 40,396
Karen L. Prus	Reg. No. 39,337		

(6) That any inquiries and correspondence relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

The undersigned further declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 5,590,645 and any extensions thereof.

Glaxo Group Limited,

November 1, 1997
Date

By: Graham George Brereton
Attorney for Glaxo Group Limited

EXHIBIT 2

Assignment of
Application for Letters Patent of the United States

No. 663,145 abandoned in favor of continuation application
No. 175,174 abandoned in favor of continuation application
No. 552,166 which issued as

U.S. Patent 5,590,645

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: DARBY & DARBY
805 THIRD AVENUE
NEW YORK, NY 10022

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 DAVIES, MICHAEL B.	DOC DATE: 02/15/91
ASSIGNOR: 002 HEARNE, DAVID J.	DOC DATE: 02/15/91
ASSIGNOR: 003 RAND, PAUL K.	DOC DATE: 02/15/91
ASSIGNOR: 004 WALKER, RICHARD I.	DOC DATE: 02/15/91

RECORDATION DATE: 03/15/91 NUMBER OF PAGES 004 REEL/FRAME 5645/0202

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 GLAXO GROUP LIMITED, CLARGES HOUSE, 6/12 CLARGES ST., LONDON W1Y 8DH, ENGLAND

SERIAL NUMBER	7-663145	FILING DATE	03/01/91
PATENT NUMBER		ISSUE DATE	00/00/00

8.00-518 HD

CERTIFICATE OF MAILING

I hereby certify that this paper and every paper referred to therein as being enclosed herewith is being deposited with the U.S. Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner of Patents & Trademarks, Washington, DC 20231, on MARCH 13, 1991 (Date of Deposit)

3/13/91 Donna Gundrey
Date Name

File No: 2954/06403

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

MICHAEL BIRSHA DAVIES, DAVID JOHN HEARNE, PAUL KENNETH RAND and RICHARD IAN WALKER

Serial No: 663,145 Group Art Unit:

Filed: 1 March 1991 Examiner:

For: INHALATION DEVICE

RECEIVED
MAR 22 1991
APPLICATION DIVISION

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

RECORDED: 04/01/1991
REEL 5645 FRAME 202

COMPLETION OF PATENT APPLICATION

This following items are submitted herewith in completion of the above-identified patent application:

1. [X] Declaration, petition and power of attorney (with copy of specification)

2. [X] Check in the amount of $878.00, (X filing; X recording) (See attached Fee Computation Sheet)

3. [X] Informal drawings, 28 sheets (Figs. 1-35) 93182860

4. [X] Assignment for recording to: GLAXO GROUP LIMITED

Priority is claimed for this application, corresponding application/s having been filed as follows:

Country : United Kingdom
Number : 90 04781.2
Date : 2 March 1990

01 MR 03/01/91 07663145 1 518 8.00 CH

RECEIVED
91 APR -1 AM 6:53
ASSIGNMENT BRANCH

The priority documents [X] are enclosed

The Patent Office is authorized to charge any deficiency up to $300.00 in the above fees, and to credit any excess, to our Deposit Account No. 4-0100.

Respectfully submitted,

Dated: 13 March 1991

Paul Fields
Reg. No. 20,298
Attorney for Applicant(s)

DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022
212-527-7700

File No: 2954/06403

PATENT FEE COMPUTATION SHEET

	No. of Claims Presented		Extra Claims Previously Paid For		Number of Extra Claims		Rate		
Basic Fee									$630.00
Total Claims	26	-20 -	0	=	6	x	$20	=	$120.00
Independent Claims:	2	- 3 -	0	=	0	x	$60	=	$ -0-
Multiple Dependent Claims Presented:	If so, add						$120	=	$ -0-
TOTAL FILING FEE									$750.00

Surcharge for late submission of filing fee and/or declaration ($120)	$120.00
SUBTOTAL	$870.00
[ ] Small Entity REDUCTION (Half of Subtotal)	$ -0-
Fee for recordation of assignment ($8.00)	$ 8.00
Charge for filing application non-English Language ($30.00)	$ -0-
TOTAL	$878.00

A S S I G N M E N T

For good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, We,

MICHAEL BIRSHA DAVIES, DAVID JOHN HEARNE, PAUL KENNETH RAND and RICHARD IAN WALKER, c/o Glaxo Group Research Limited, of Park Road, Ware, Hertfordshire SG12 ODG, England,

do hereby sell, assign, convey and set over to our assignees,

GLAXO GROUP LIMITED,

of Clarges House, 6/12 Clarges Street, London W1Y 8DH, England, our entire right, title and interest in and to an invention entitled

Inhalation Device

and in and to the application for Letters Patent of the United States thereon, executed on the 15th day of February 1991 by the said MICHAEL BIRSHA DAVIES, DAVID JOHN HEARNE, PAUL KENNETH RAND and RICHARD IAN WALKER, and in and to any patent or patents that may issue on said application and invention in the United States of America and foreign countries, to assist in securing which we hereby convenant and agree on behalf of ourselves, our heirs, executors and legal representatives, to execute without further compensation all papers, and assignment connected with such patent or application therefor, and we do hereby authorise and request the Commissioner of Patents to issue any patents maturing on said U.S. application to our assignee as the beneficial owner therefor;

IN WITNESS WHEREOF We have unto set our hand and seal this 15th day of February 1991

Michael Birsha Davies
MICHAEL BIRSHA DAVIES

David John Hearne
DAVID JOHN HEARNE

Paul Kenneth Rand
PAUL KENNETH RAND

Richard Ian Walker
RICHARD IAN WALKER

EXHIBIT 5

Product Description

Figure 1. Photograph of the assembled device

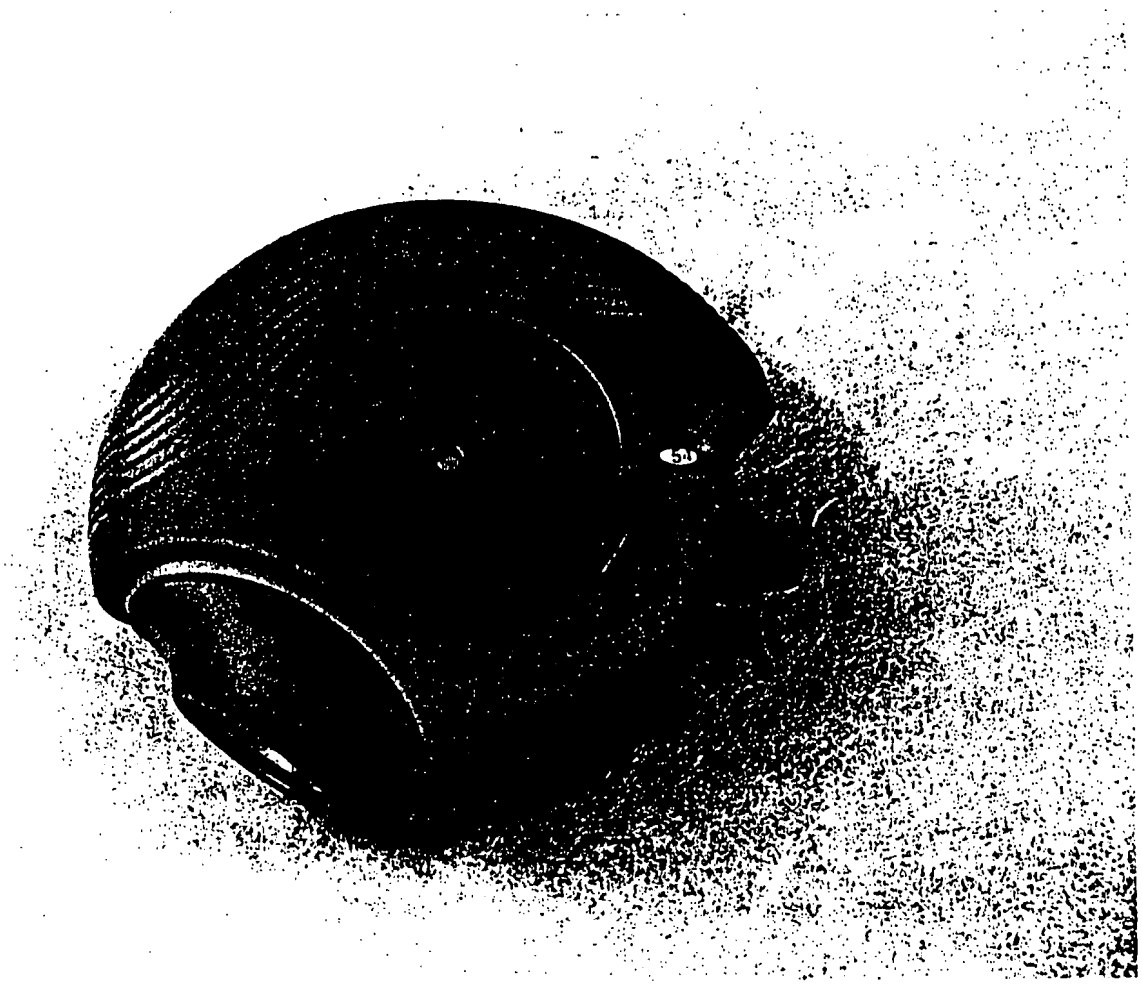


Figure 2. Photograph of foil strip inside the Diskus device

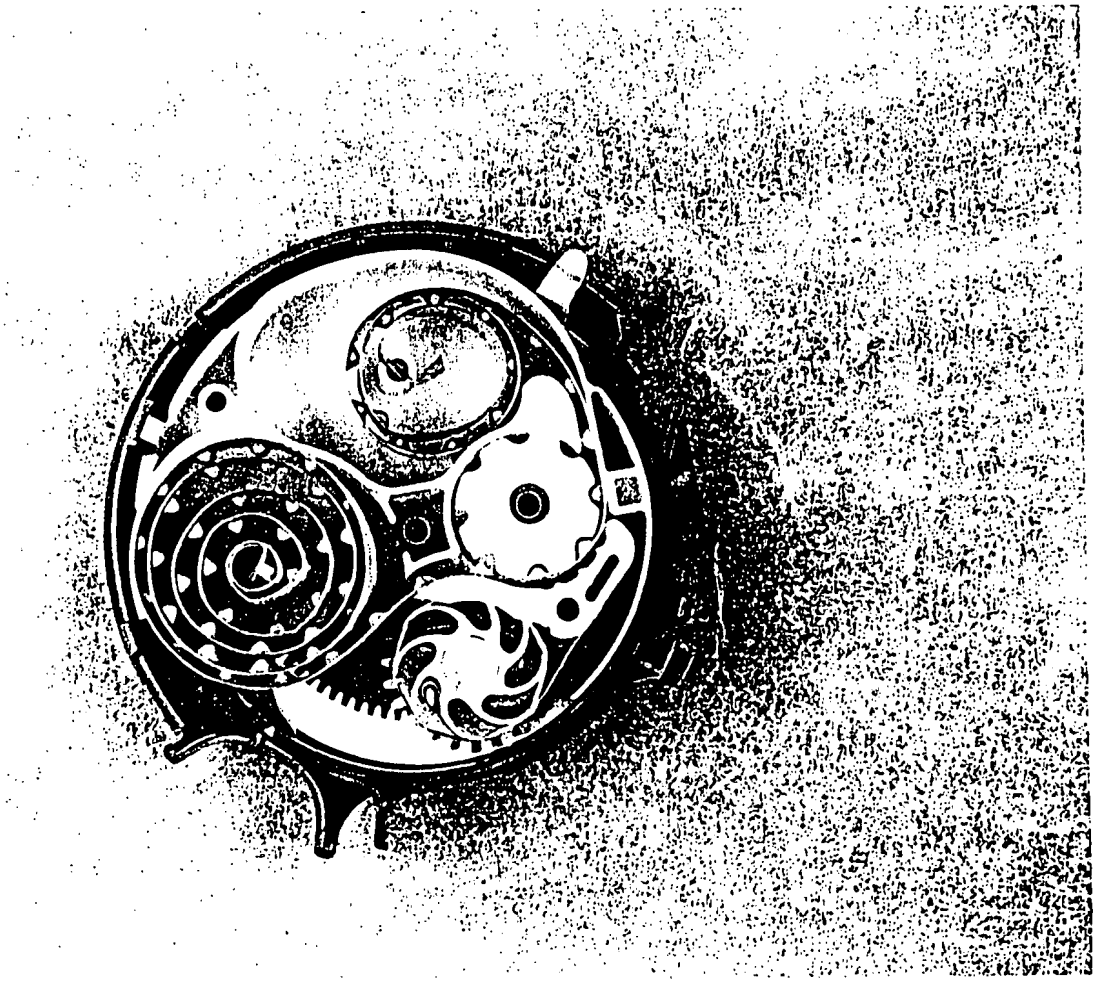


Figure 3. Photograph of a foil strip

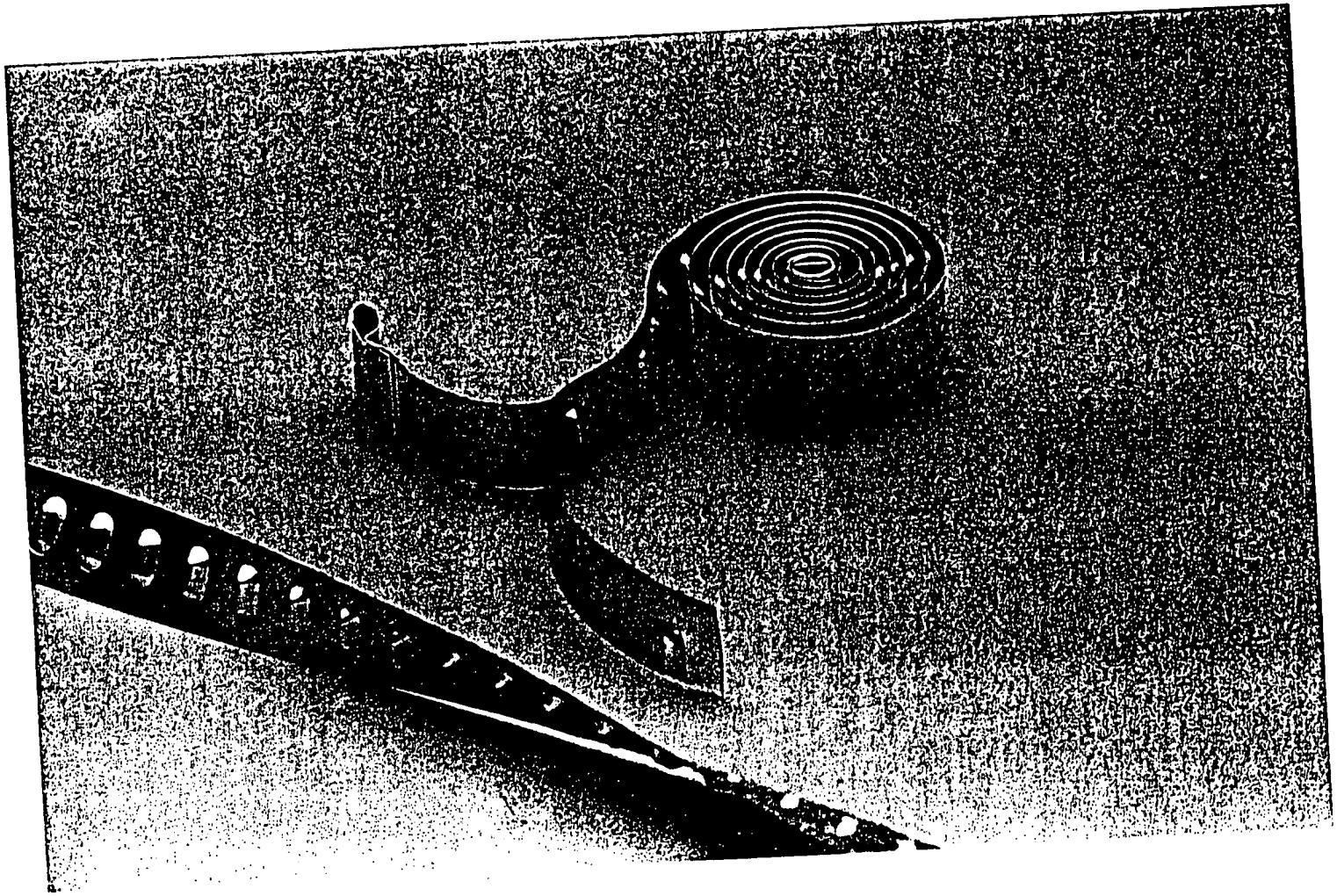
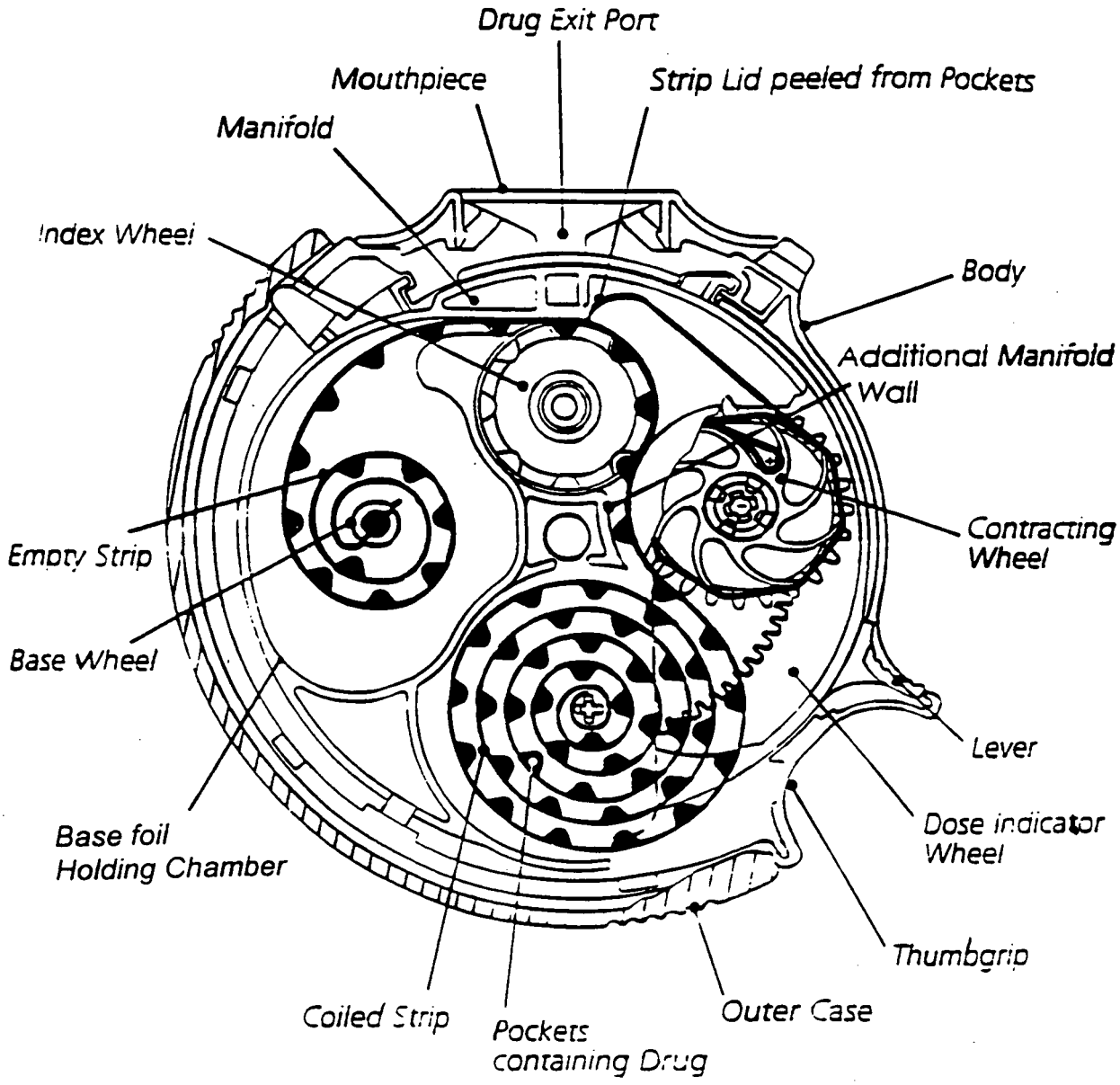


Figure E6. Diagrammatic representation of the inside of the Diskus device



Cross Section through Device

Figure E7. Diagram of the Diskus device

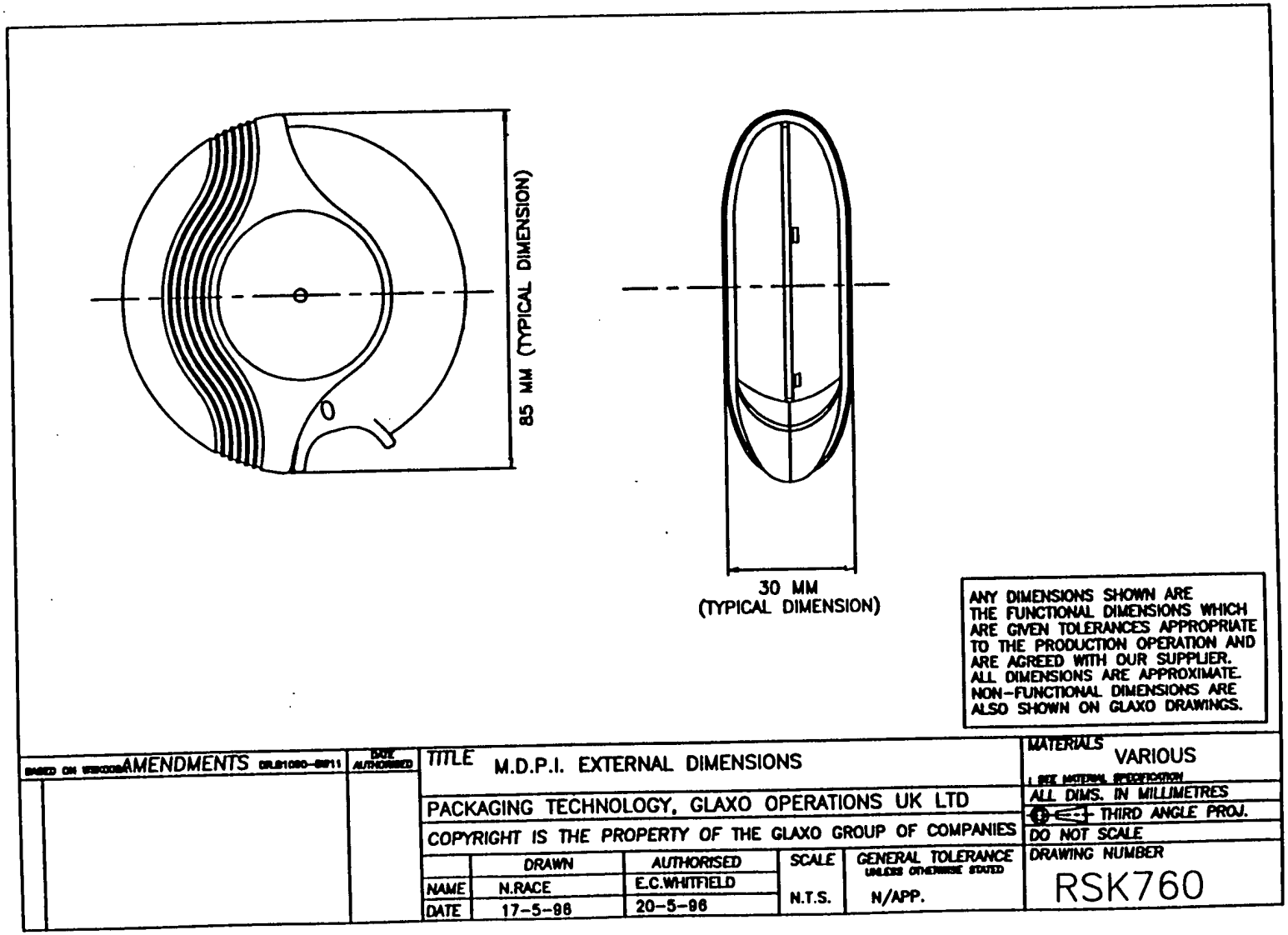


Figure E8. Exploded diagram of the Diskus device (RSK614A)

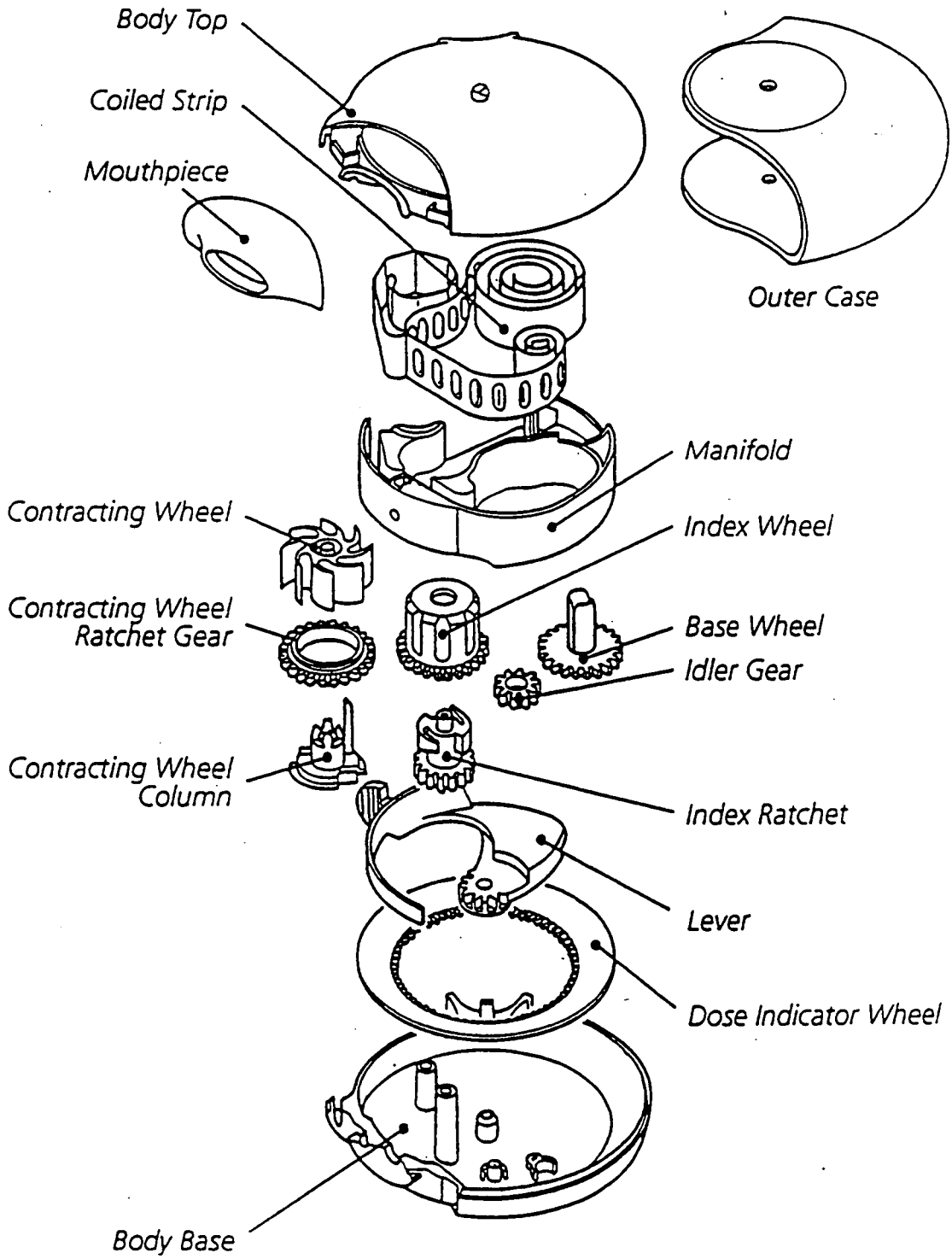


Figure E9. Diagram of the index wheel of the Diskus device

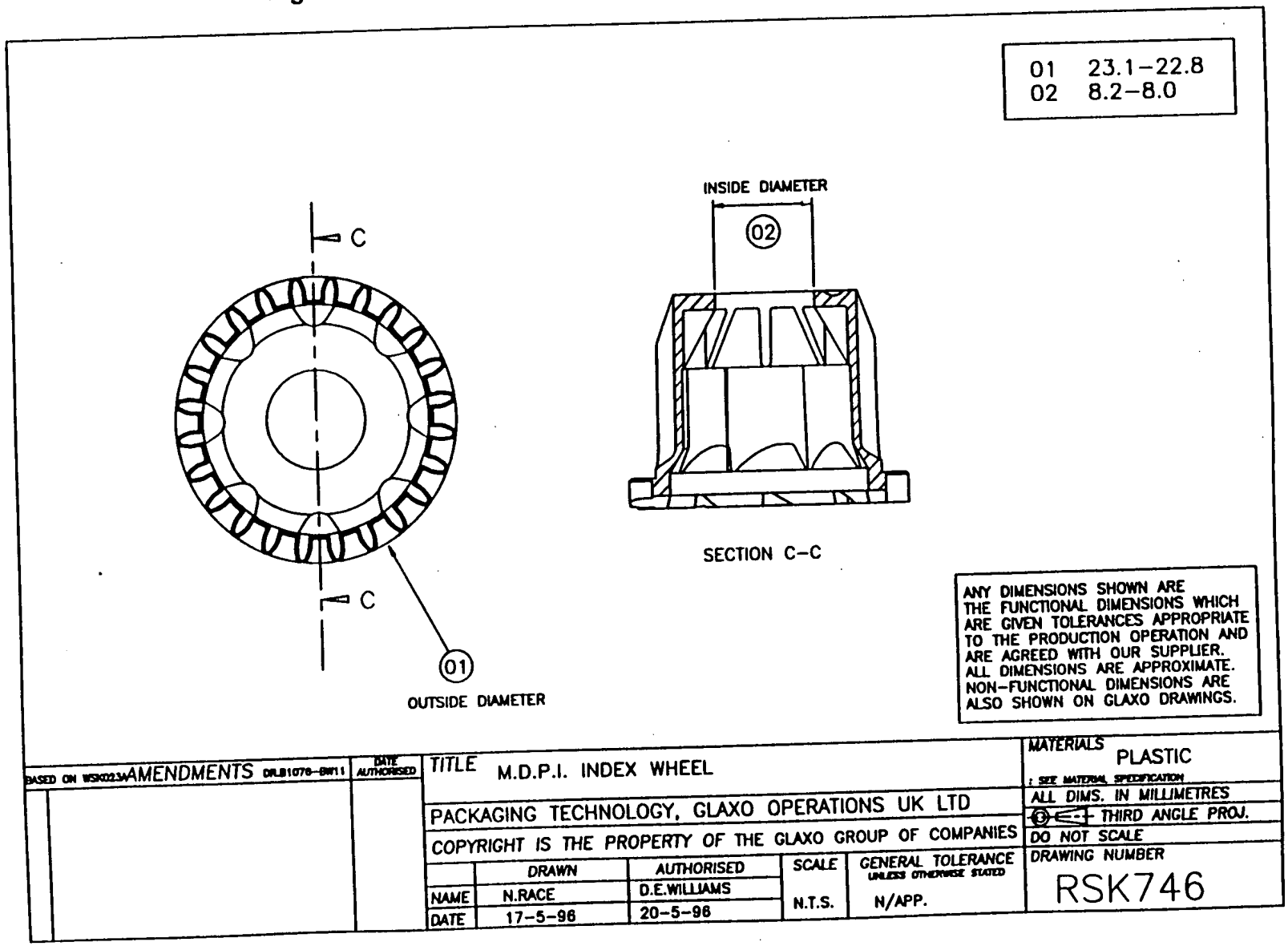
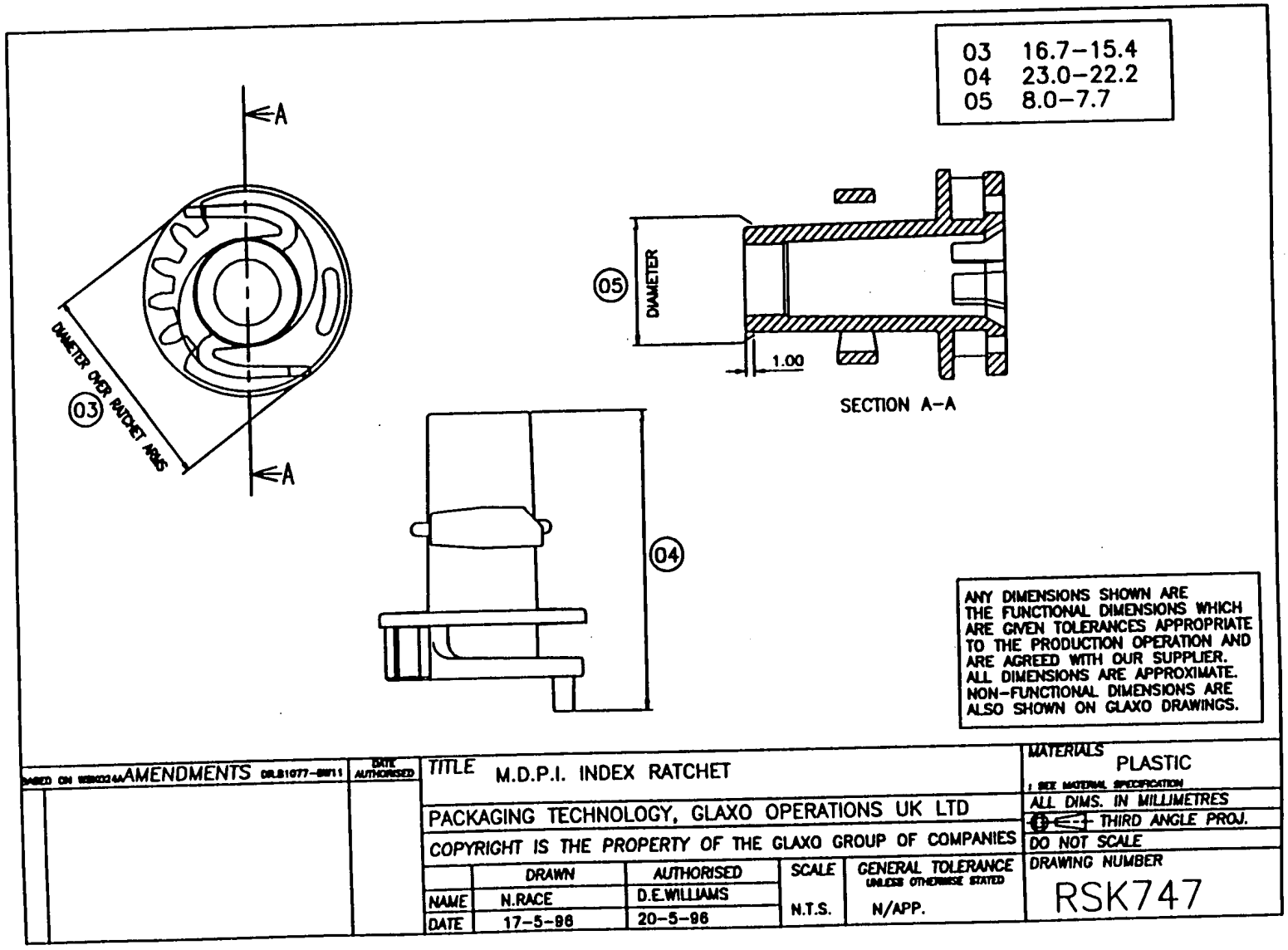
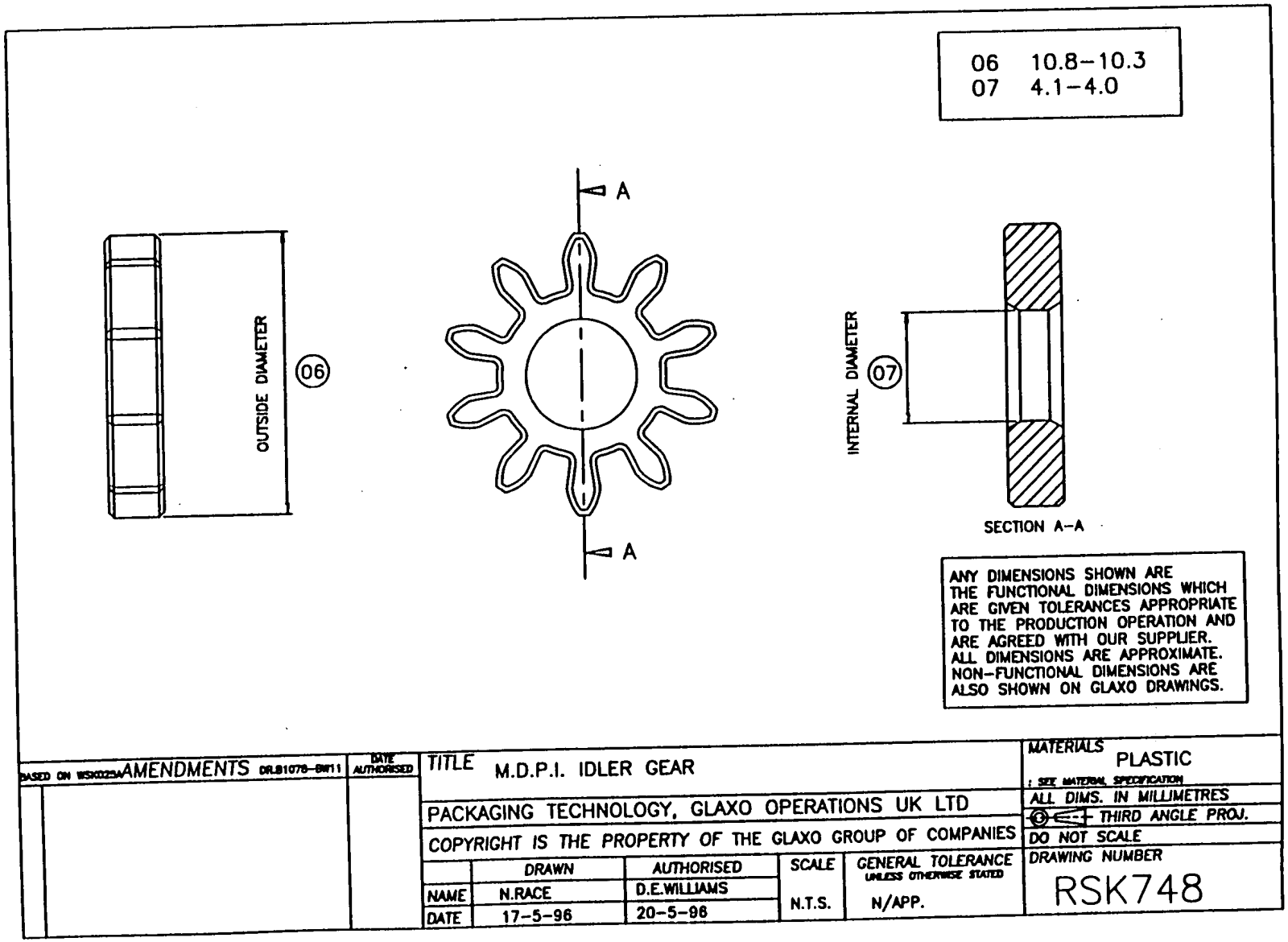


Figure E10. Diagram of the index ratchet of the Diskus device



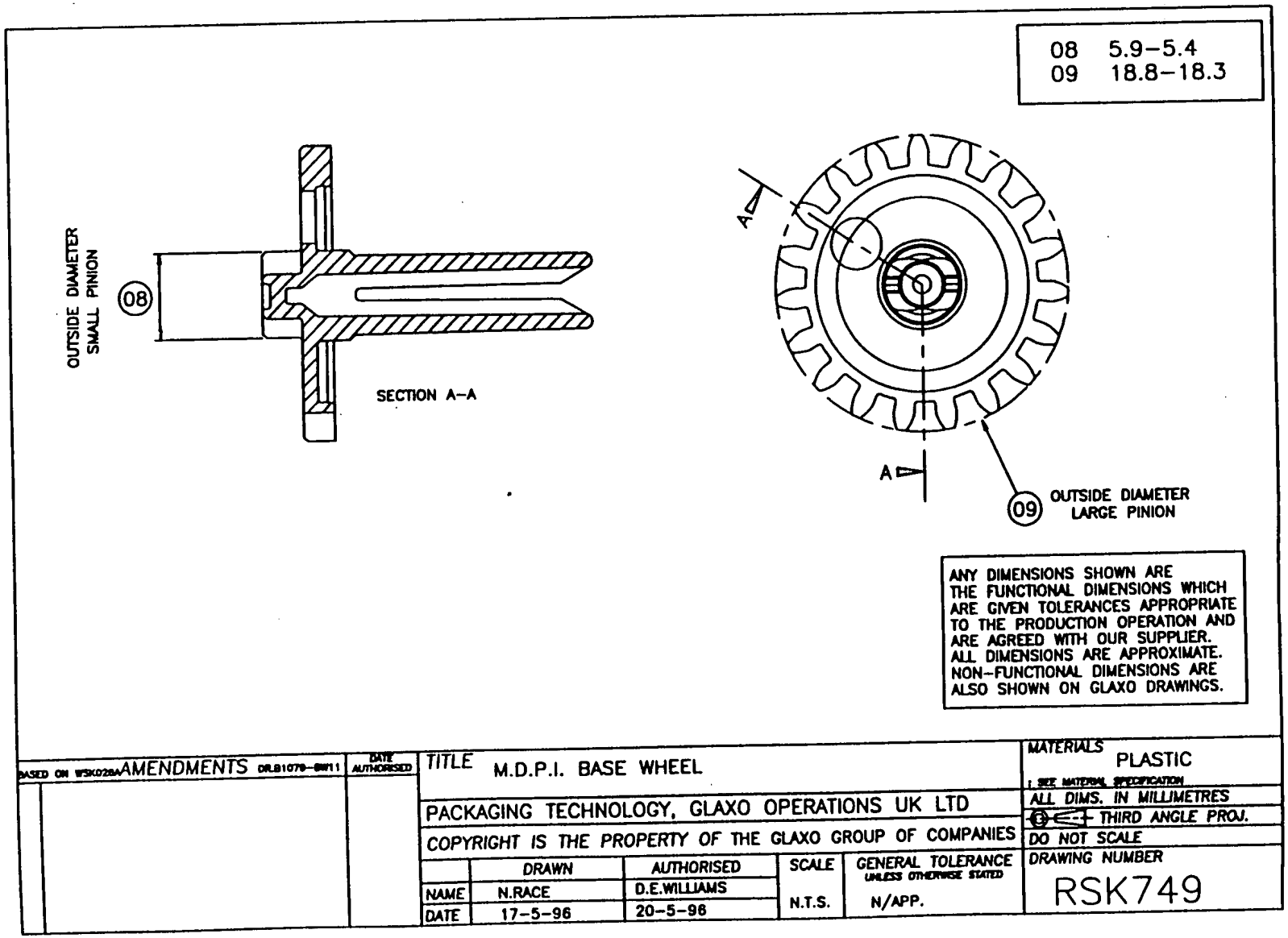
T:\201PI\NDA\US95145\FIGE10.DOC

Figure E11. Diagram of the idler gear of the Diskus device



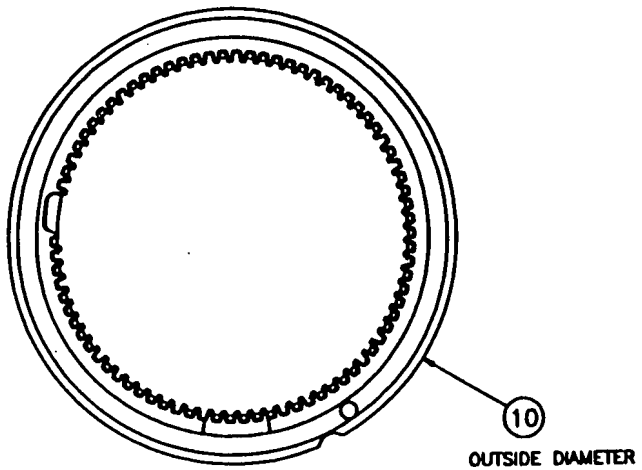
T:\201PI\NDA\US95145\FIGE11.DOC

Figure E12. Diagram of the base wheel of the Diskus device



T:\201PI\NDA\US95145\FIGE12.DOC

Figure E13. Diagram of the dose indicator wheel of the Diskus device

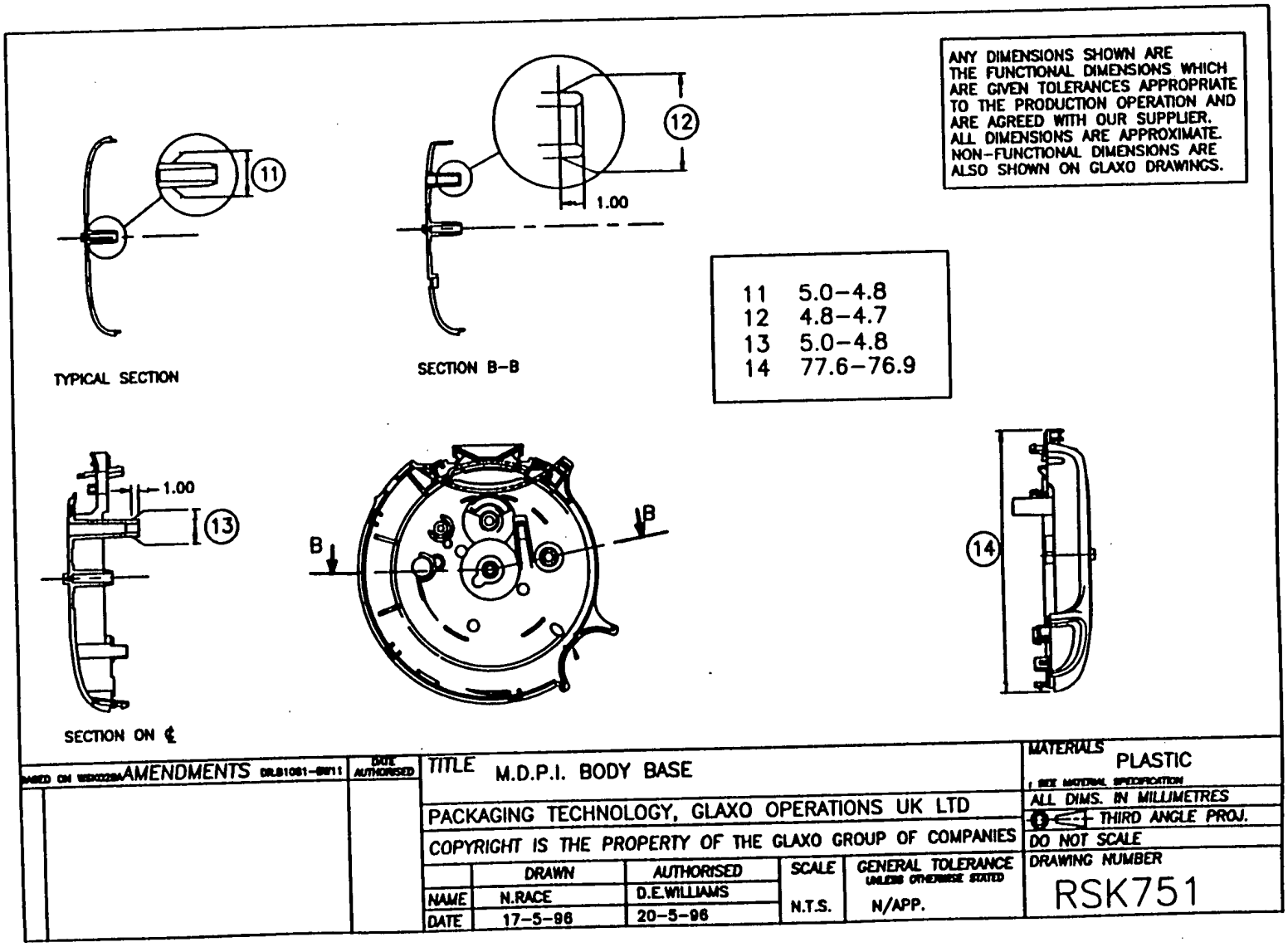


10	59.5–59.0

ANY DIMENSIONS SHOWN ARE THE FUNCTIONAL DIMENSIONS WHICH ARE GIVEN TOLERANCES APPROPRIATE TO THE PRODUCTION OPERATION AND ARE AGREED WITH OUR SUPPLIER. ALL DIMENSIONS ARE APPROXIMATE. NON-FUNCTIONAL DIMENSIONS ARE ALSO SHOWN ON GLAXO DRAWINGS.

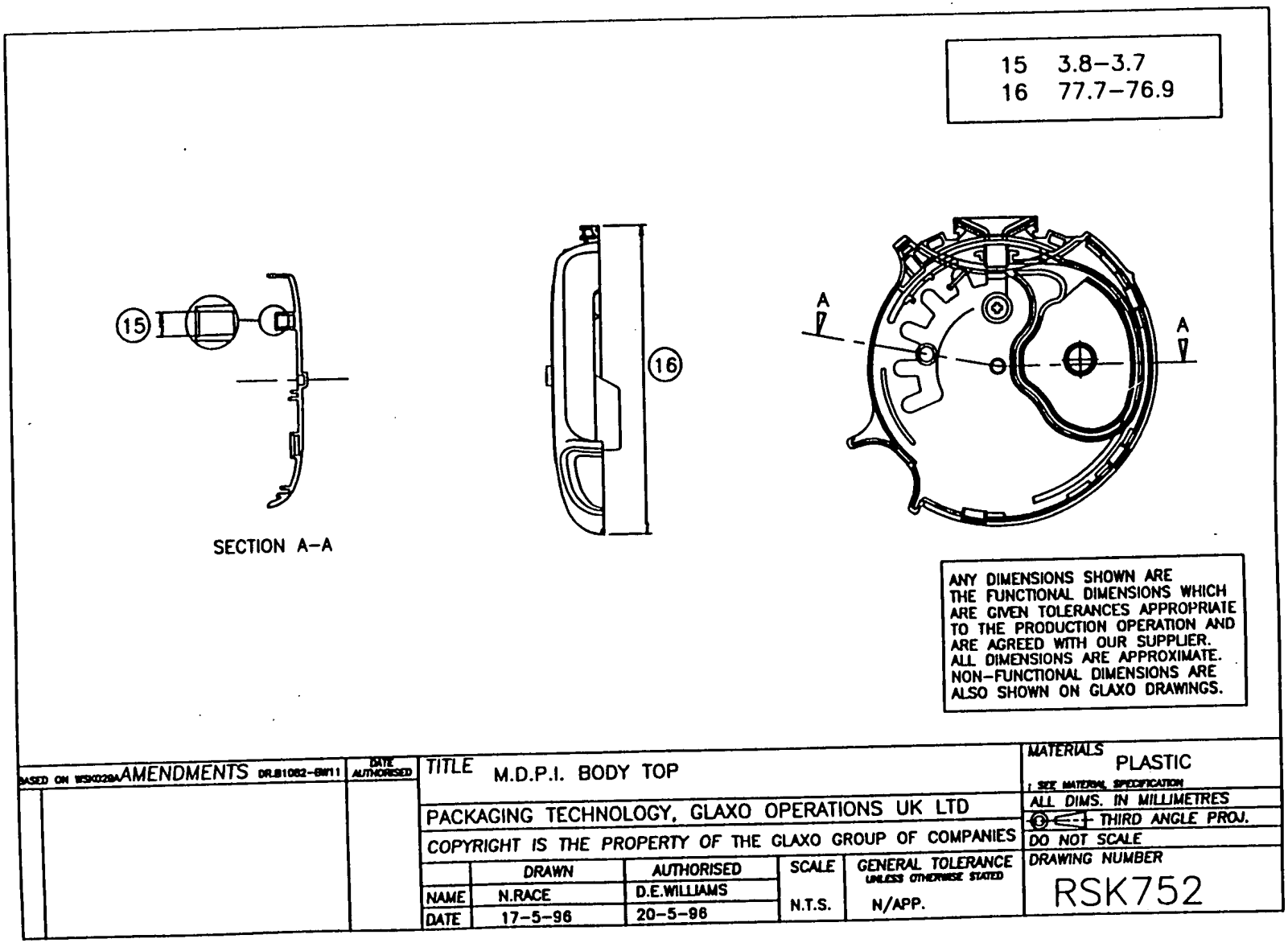
BASED ON W80027A AMENDMENTS DR.91080-BW11	DATE AUTHORISED	TITLE M.D.P.I. DOSE INDICATOR WHEEL			MATERIALS PLASTIC
		PACKAGING TECHNOLOGY, GLAXO OPERATIONS UK LTD			ALL DIMS. IN MILLIMETRES
		COPYRIGHT IS THE PROPERTY OF THE GLAXO GROUP OF COMPANIES			THIRD ANGLE PROJ.
					DO NOT SCALE
	DRAWN	AUTHORISED	SCALE	GENERAL TOLERANCE UNLESS OTHERWISE STATED	DRAWING NUMBER
NAME	N.RACE	D.E.WILLIAMS	N.T.S.	N/APP.	RSK750
DATE	17-5-96	20-5-96			

Figure E14. Diagram of the body base of the Diskus device



T \201PI\NDA\US95145\FIGE14 DOC

Figure E15. Diagram of the body top of the Diskus device



T:\201P\NDA\US95145\FIGE15.DOC

Figure E16. Diagram of the mouthpiece of the Diskus device

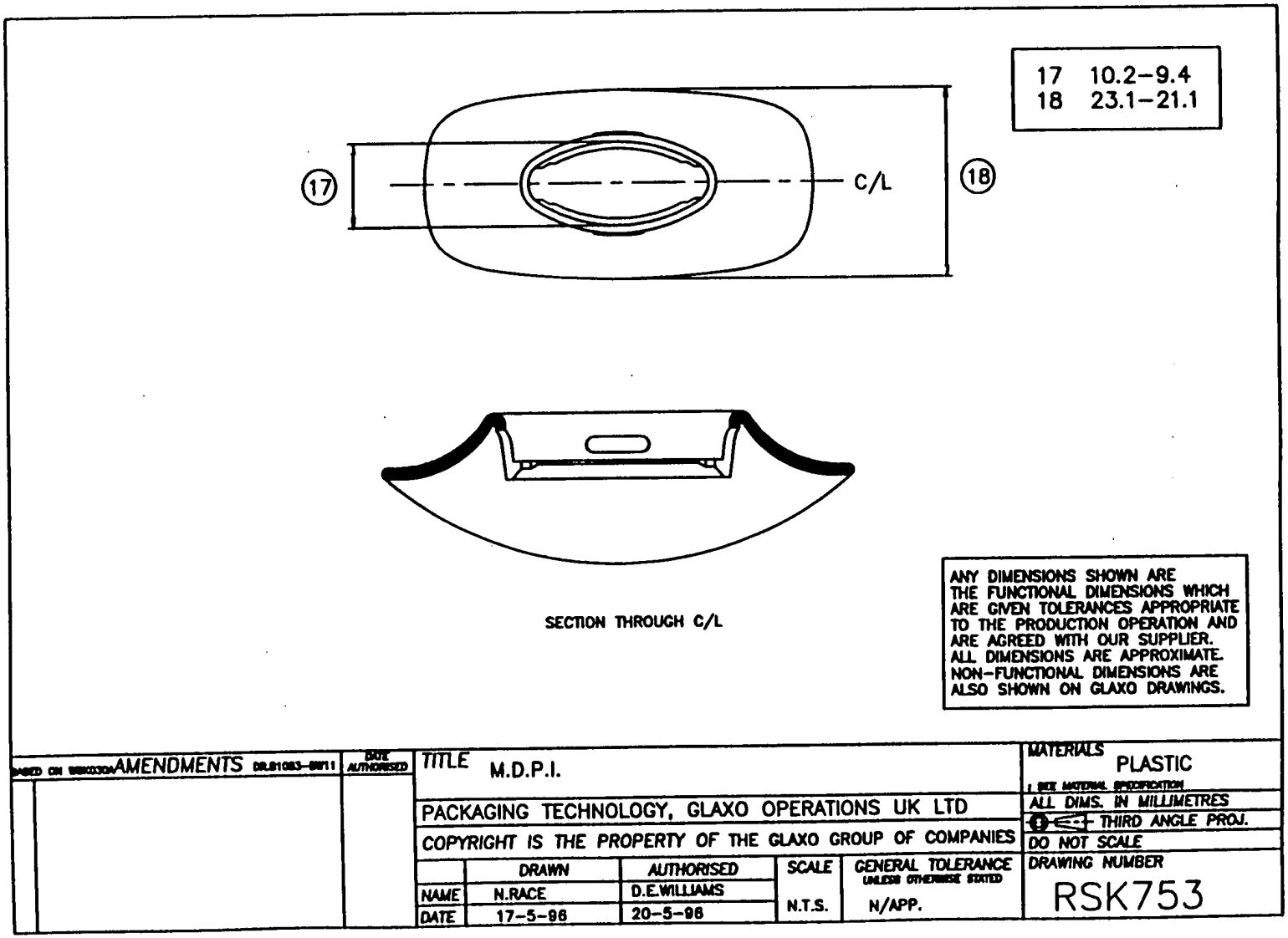
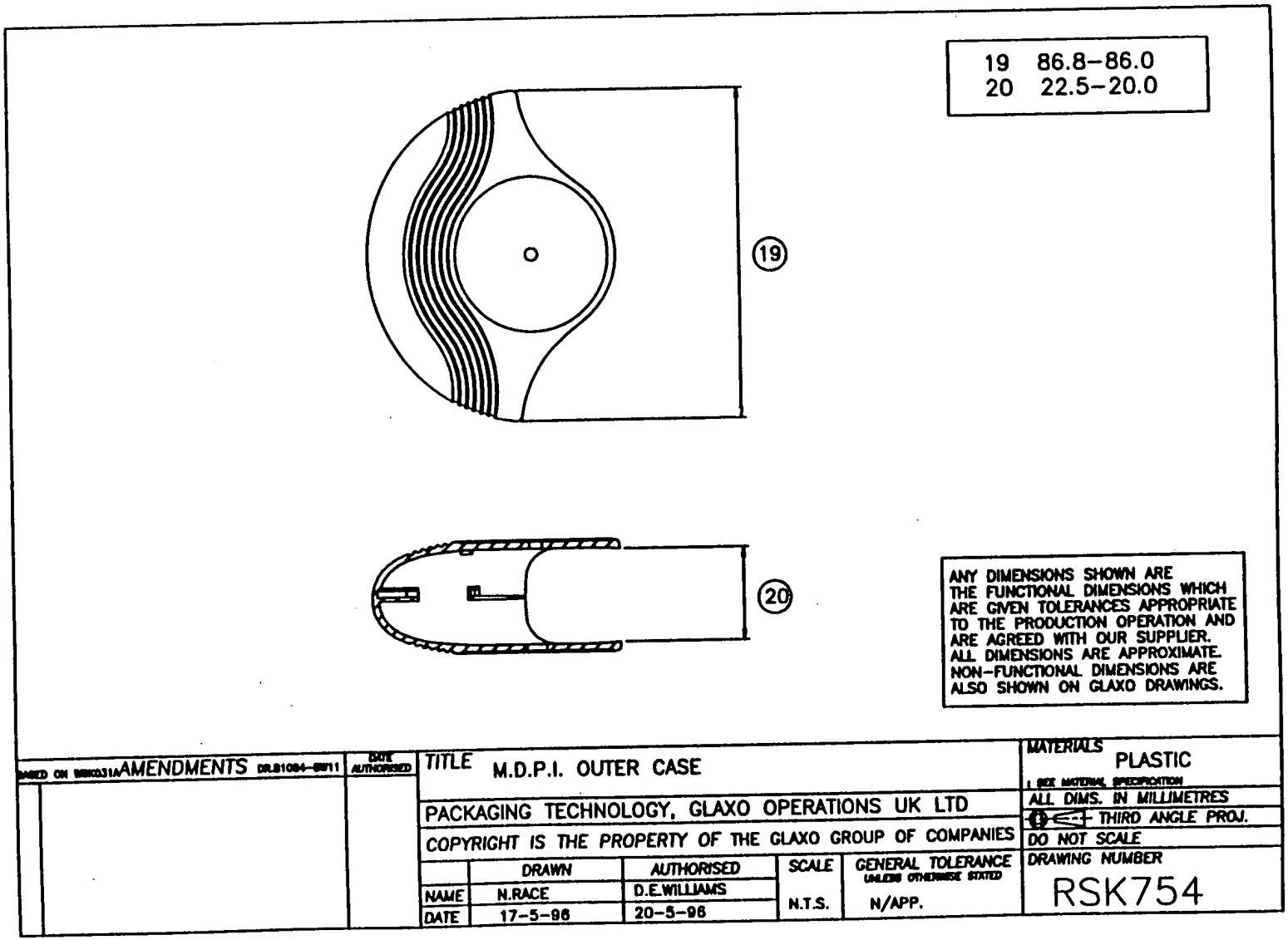
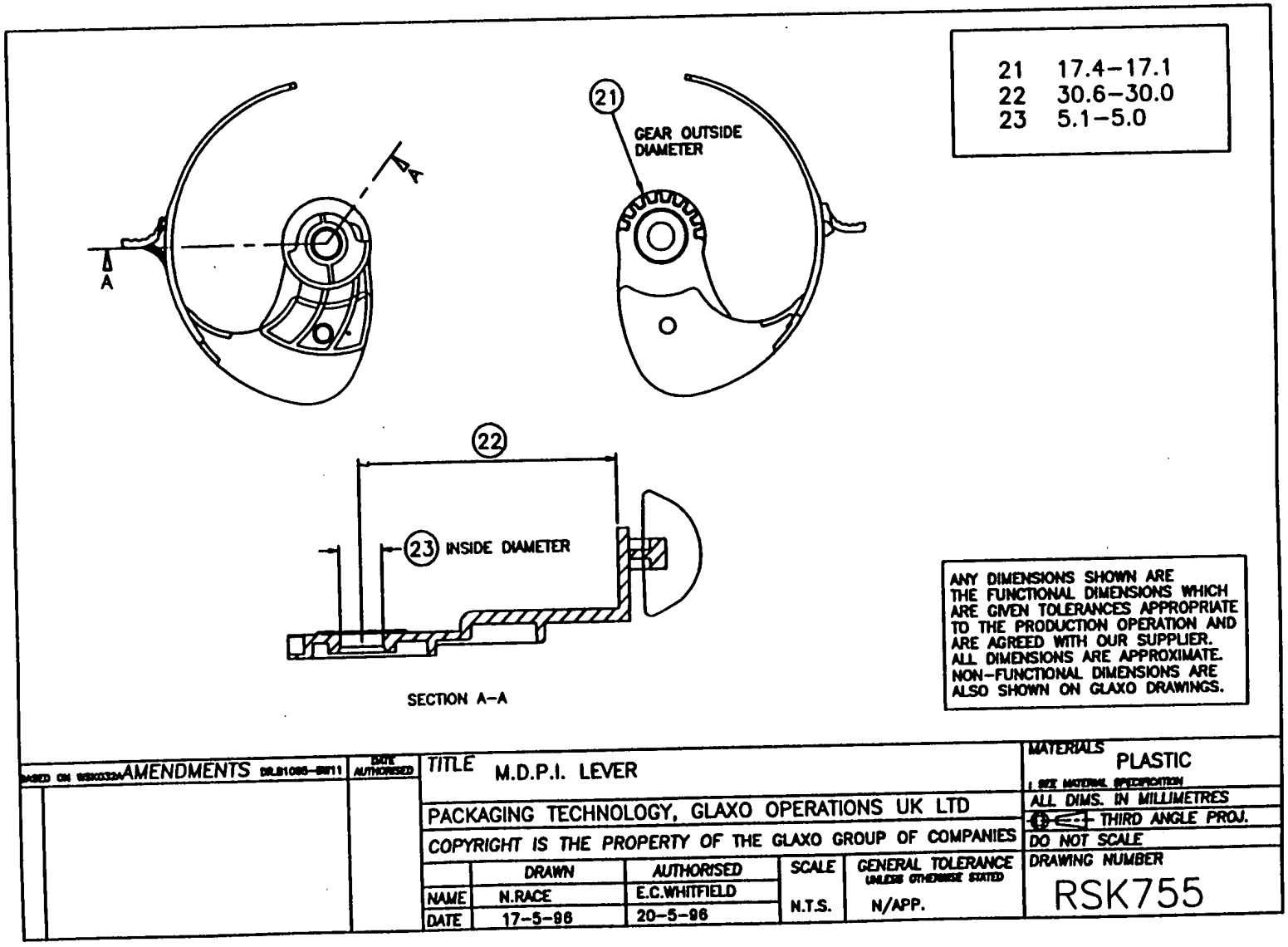


Figure E17. Diagram of the outer case of the Diskus device



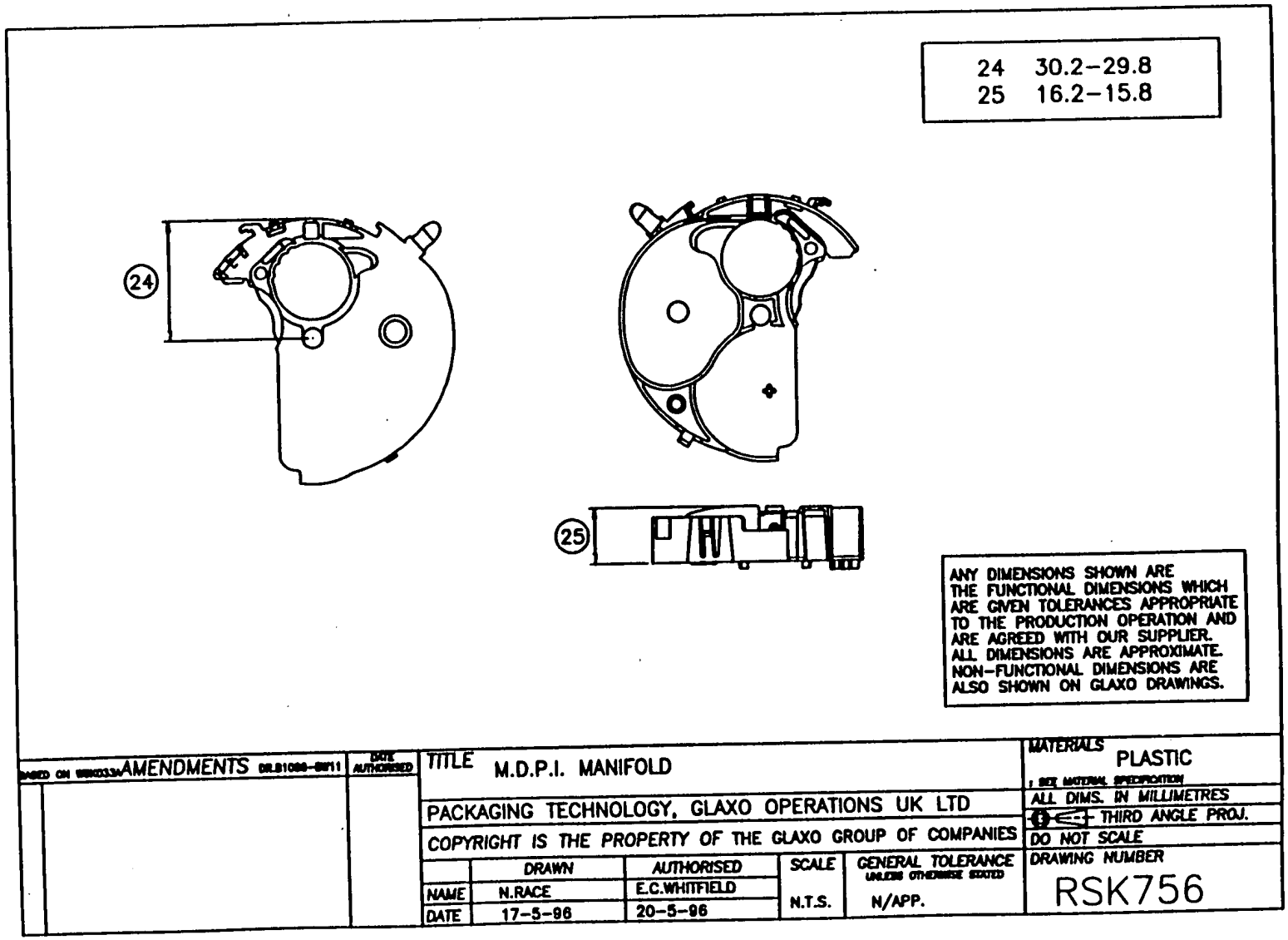
T:\201PI\NDA\US95145\FIGE17.DOC

Figure E18. Diagram of the lever of the Diskus device



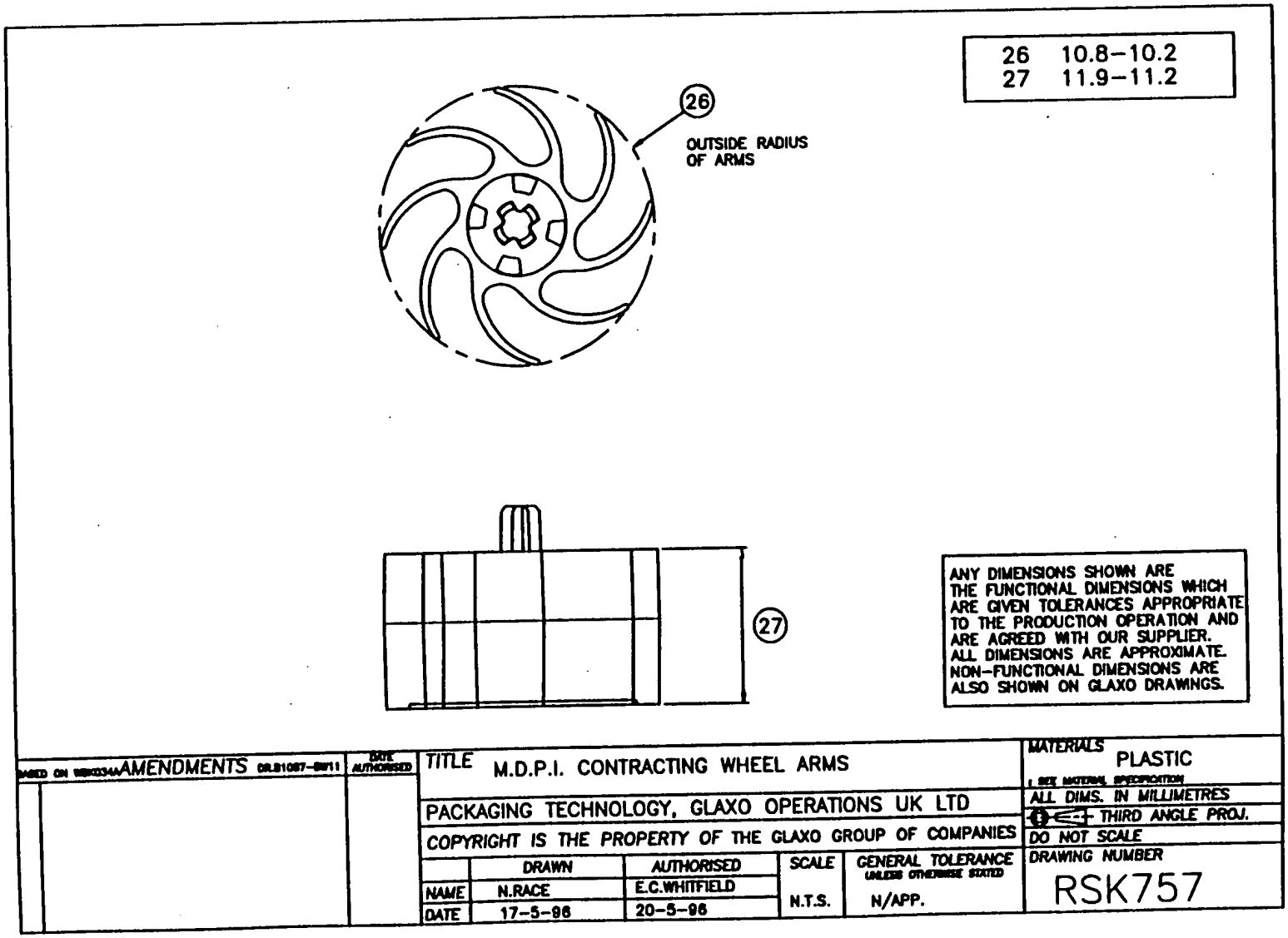
T:\201P\NDA\US95145\FIGE18.DOC

Figure E19. Diagram of the manifold of the Diskus device



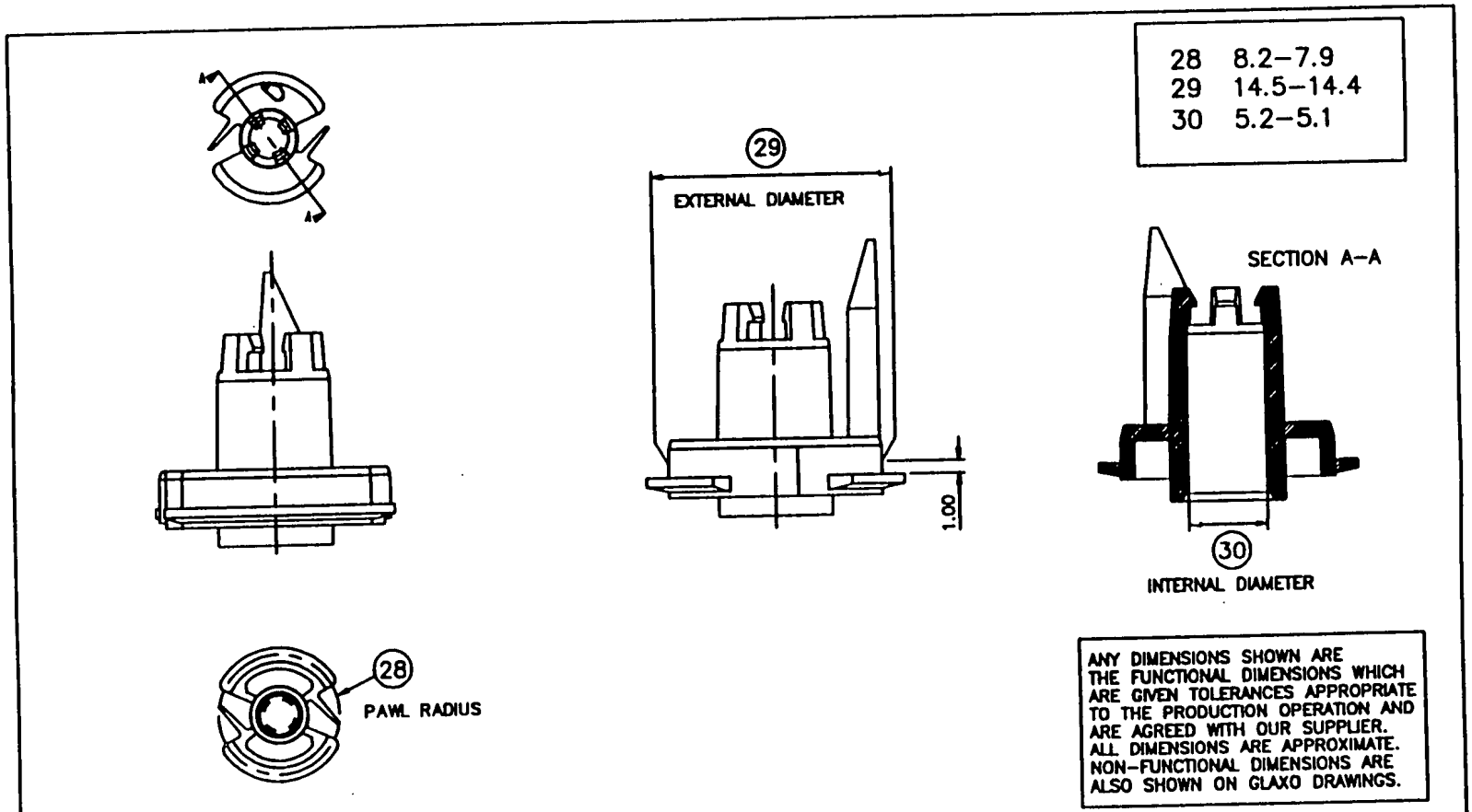
T:\201P\NDA\US95145\FIGE19.DOC

Figure E20. Diagram of the contracting wheel arms of the Diskus device



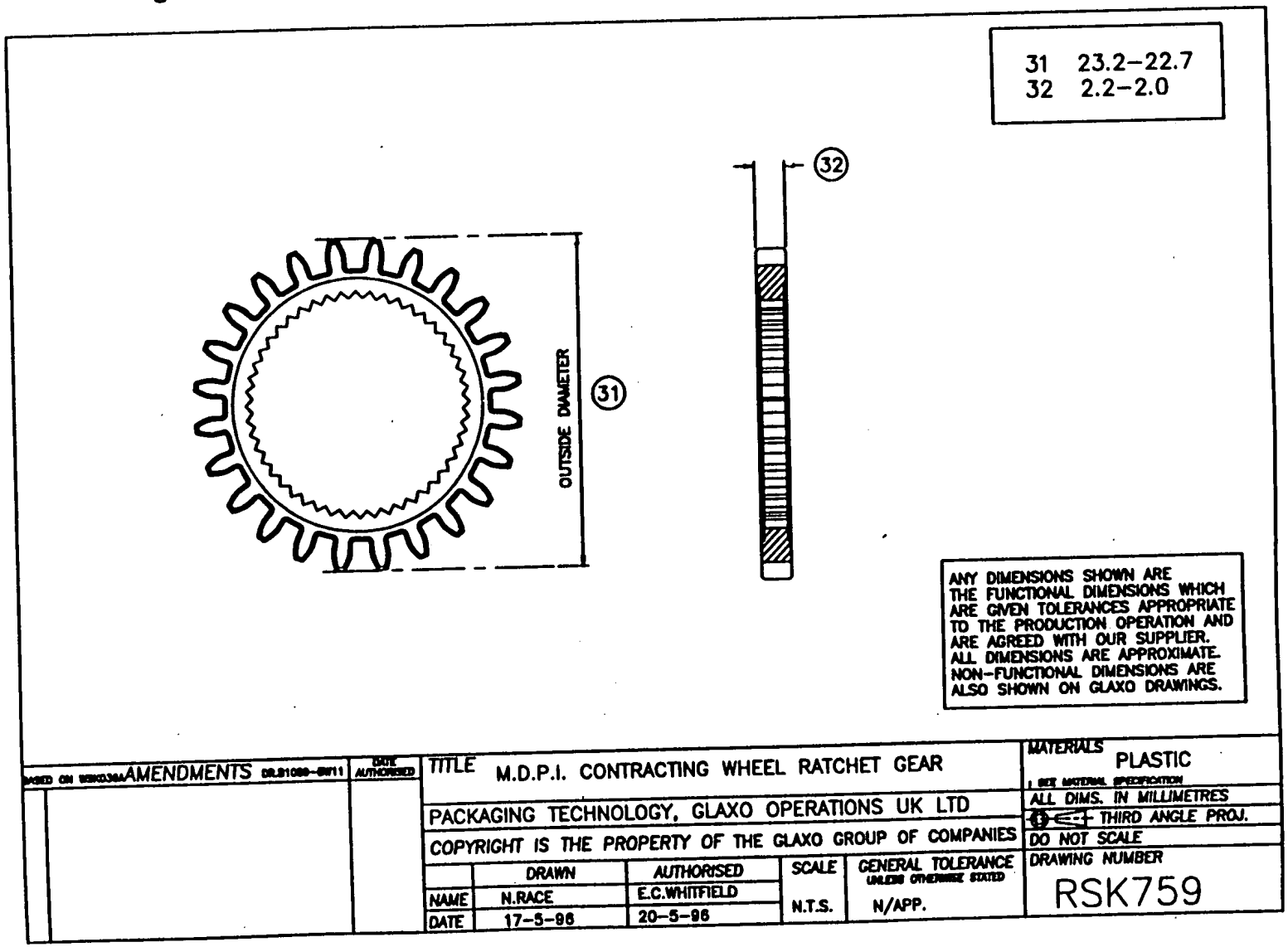
T:\201PI\NDA\US95145\FIGE20.DOC

Figure E21. Diagram of the contracting wheel column of the Diskus device



T:\201PI\NDA\US95145\FIGE21.DOC

Figure E22. Diagram of the contracting wheel ratchet gear of the Diskus device



T:\201P\NDA\US95145\FIGE22.DOC

EXHIBIT 6

U.S. Patent 5,590,645

US005590645A

United States Patent [19]

Davies et al.

[11] Patent Number: 5,590,645

[45] Date of Patent: Jan. 7, 1997

[54] **INHALATION DEVICE**

[75] Inventors: **Michael B. Davies**, Ware; **David J. Hearne**, Luton; **Paul K. Rand**, Letchworth; **Richard I. Walker**, Ware, all of England

[73] Assignee: **Glaxo Group Limited**, London, England

[21] Appl. No.: **552,166**

[22] Filed: **Nov. 2, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 175,174, Dec. 28, 1993, abandoned, which is a continuation of Ser. No. 663,145, Mar. 1, 1991, abandoned.

[30] **Foreign Application Priority Data**

Mar. 2, 1990 [GB] United Kingdom 9004781

[51] **Int. Cl.**[6] **A61M 15/00**

[52] **U.S. Cl.** **128/203.15**; 128/203.21

[58] **Field of Search** 128/203.15, 203.21; 604/58

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Primary Examiner—Aaron J. Lewis
Attorney, Agent, or Firm—Darby & Darby, P.C.

[57] **ABSTRACT**

An inhalation device is described for use with a medicament pack in which at least one container for medicament in powder form is defined between two sheets peelably secured to one another. The device comprises means for peeling the sheets apart at an opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale medicament in powder form from the opened container.

19 Claims, 21 Drawing Sheets

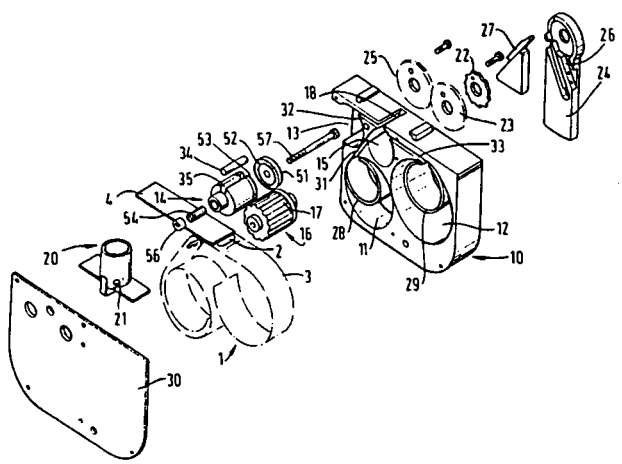

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FIG. 1

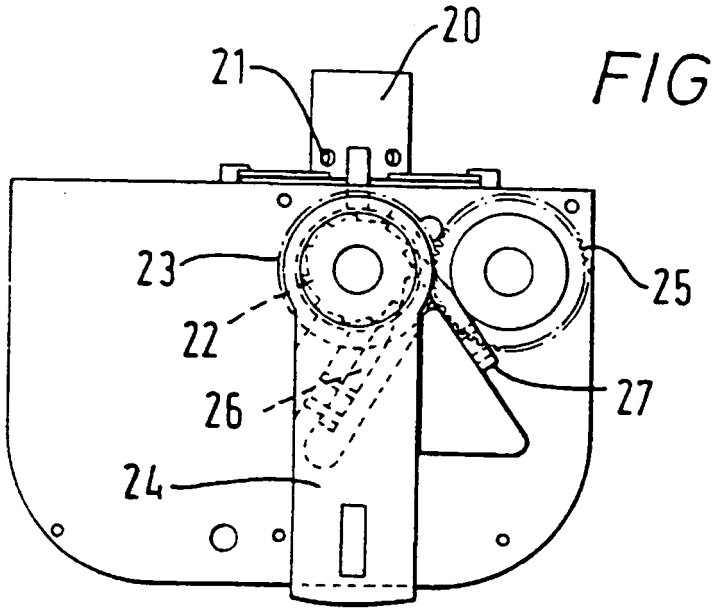


FIG. 3b

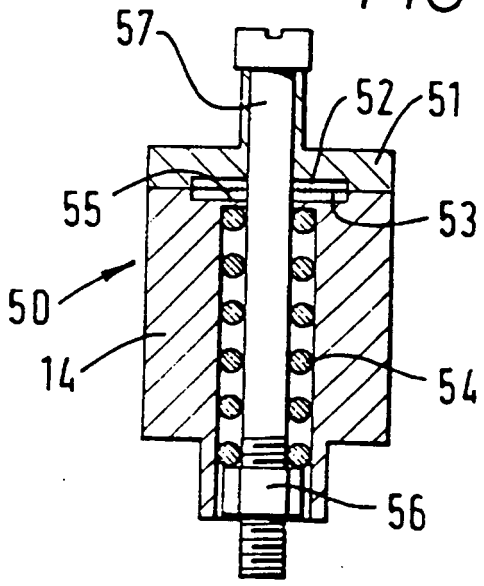


FIG. 3a

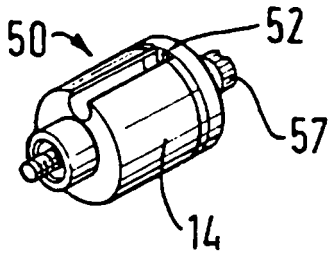
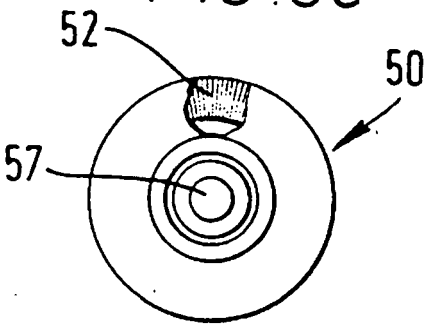


FIG. 3c



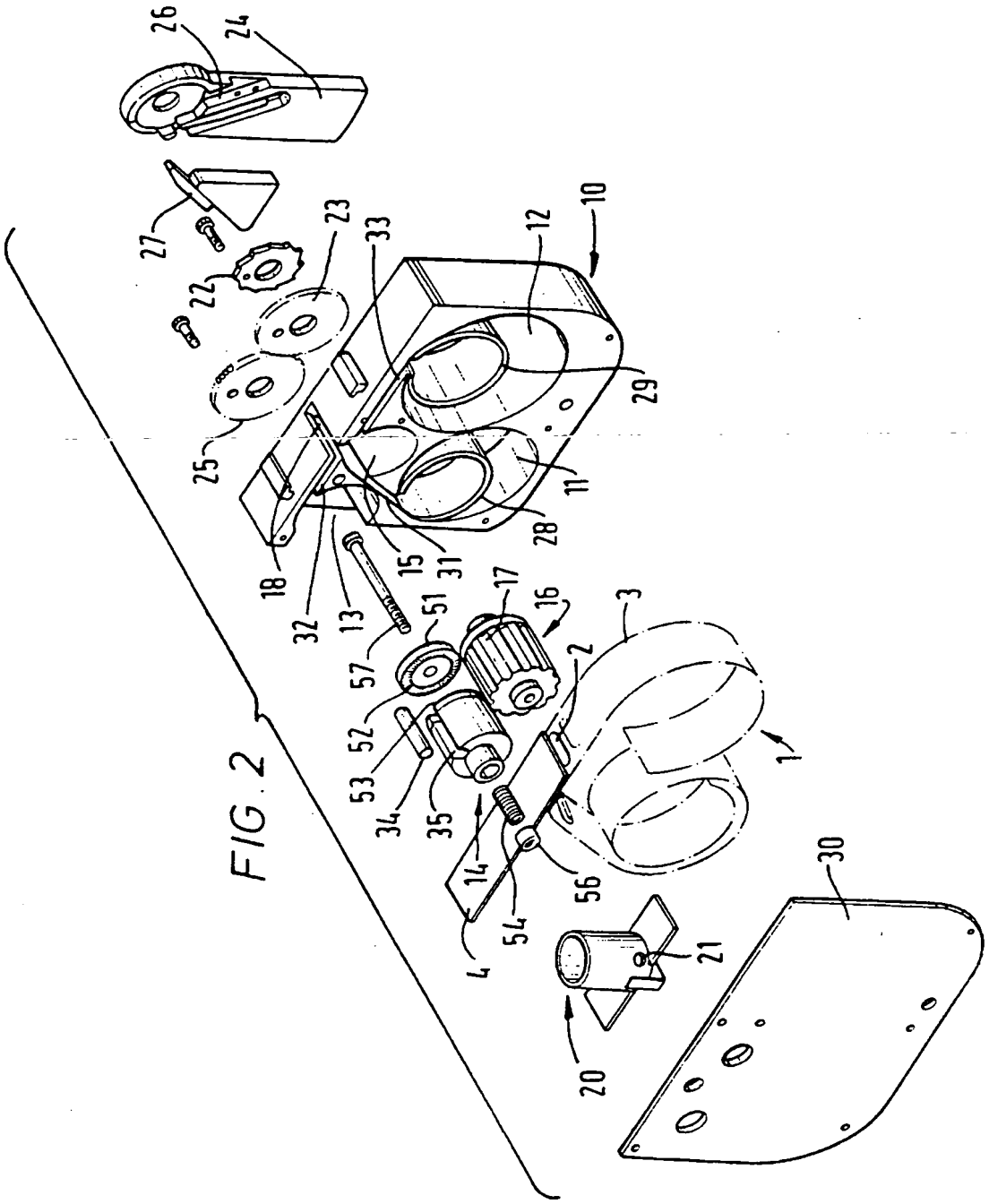

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FIG. 2

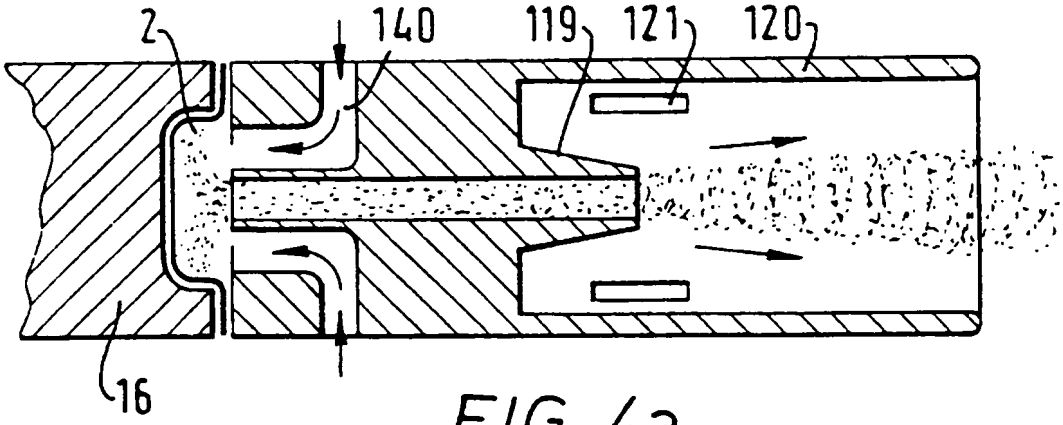


FIG. 4a

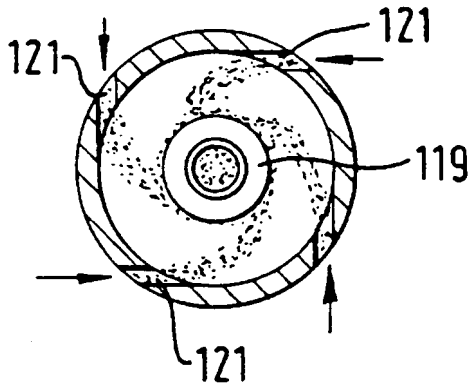


FIG. 4b

FIG. 5

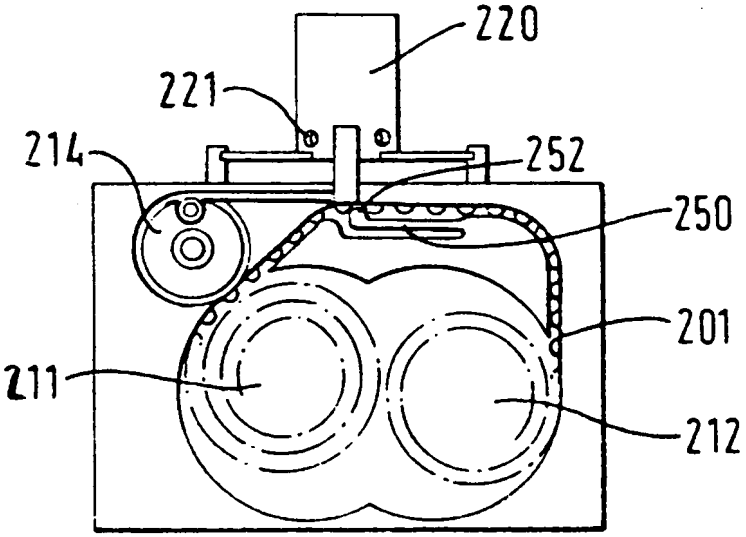


FIG. 6

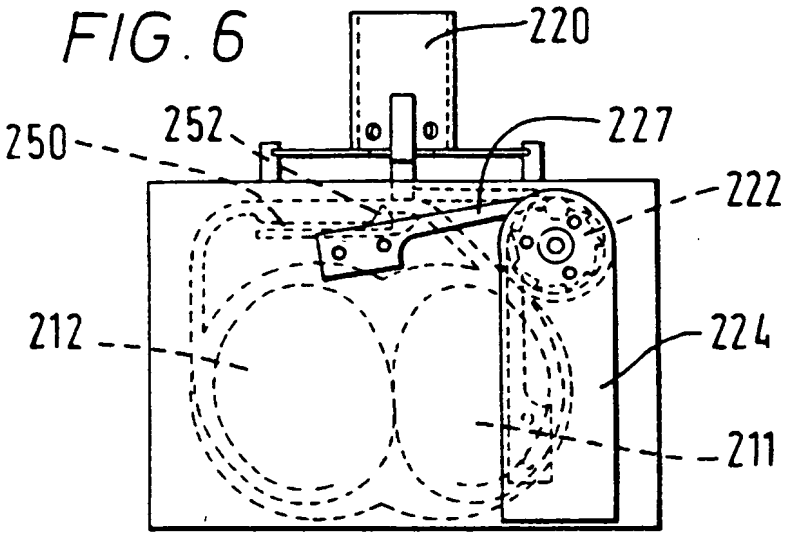


FIG. 7

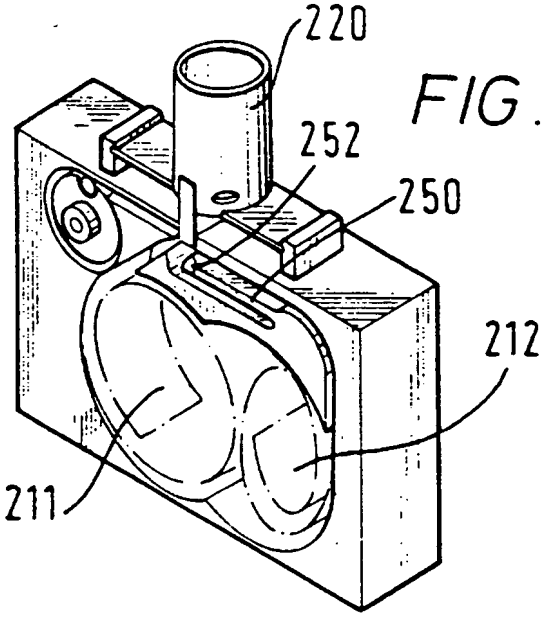


FIG. 8

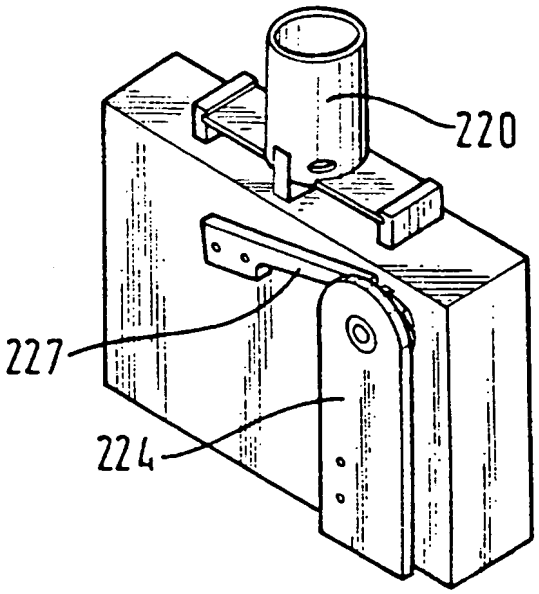


FIG.9

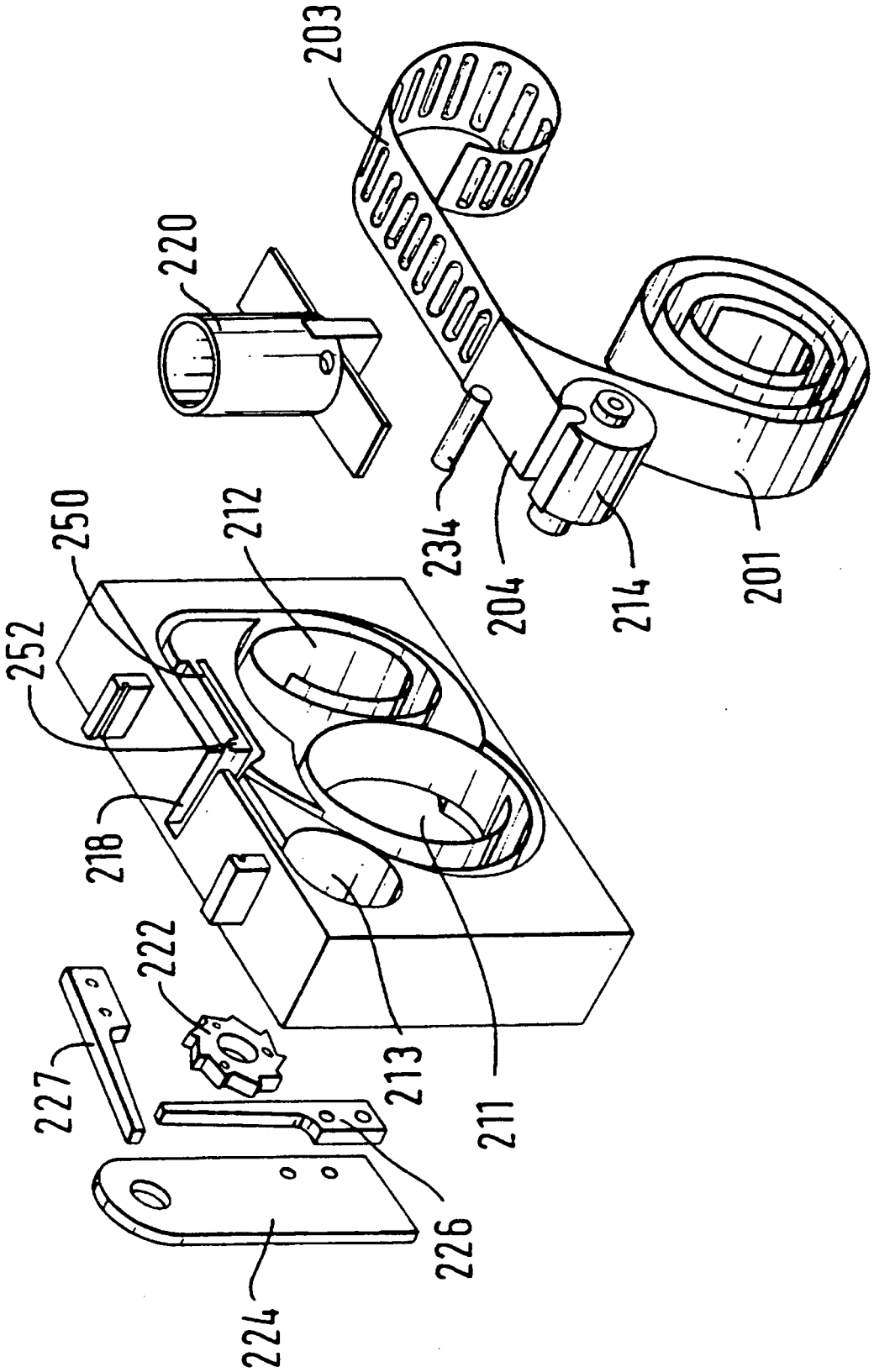


FIG. 10

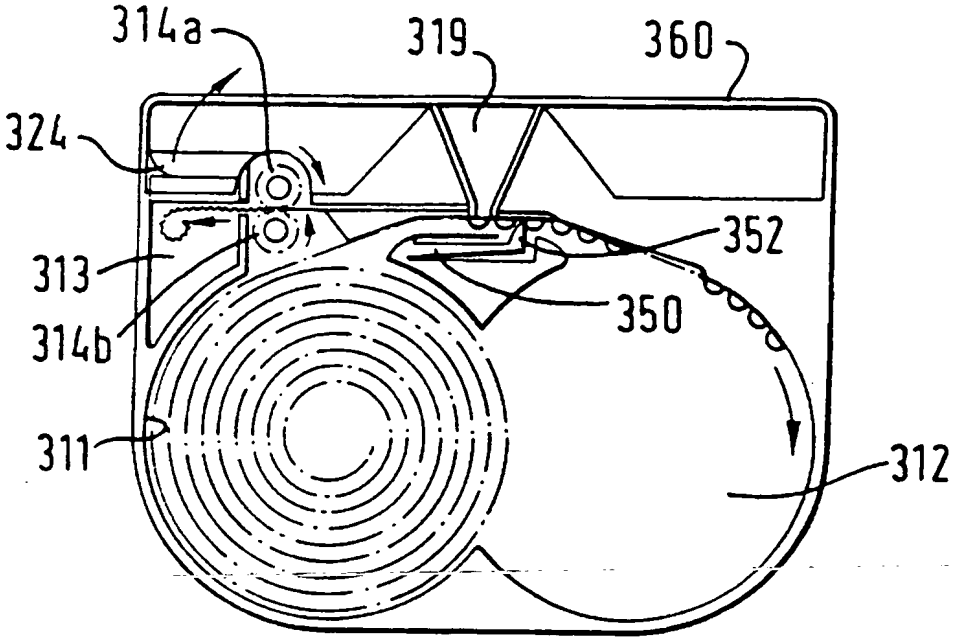


FIG. 11

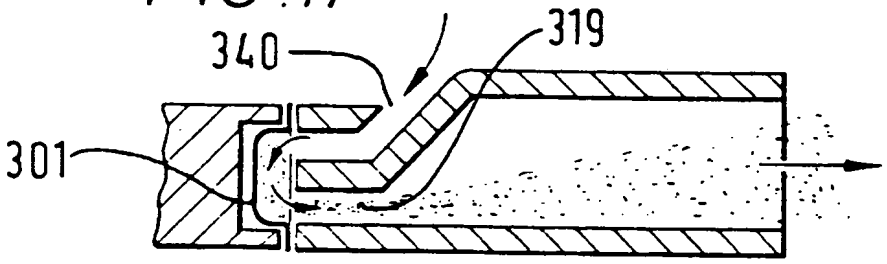


FIG. 12

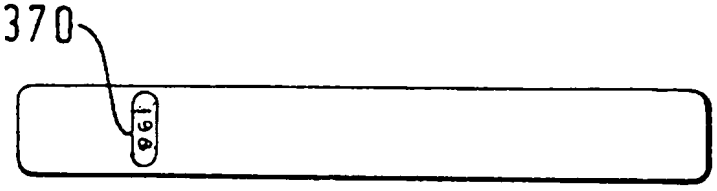


FIG.13

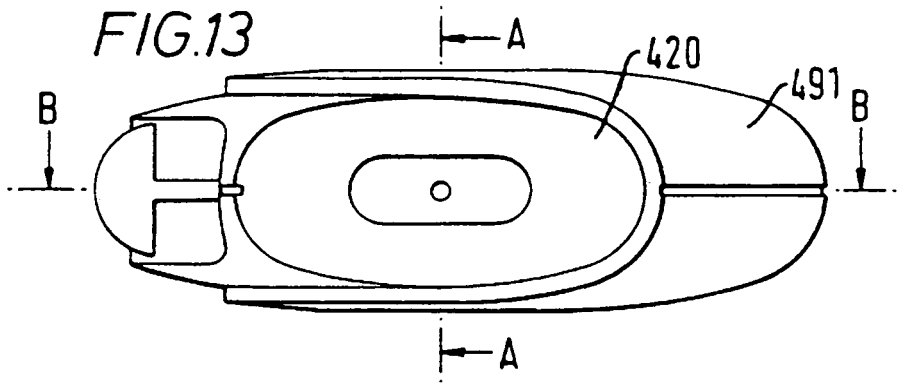


FIG.14

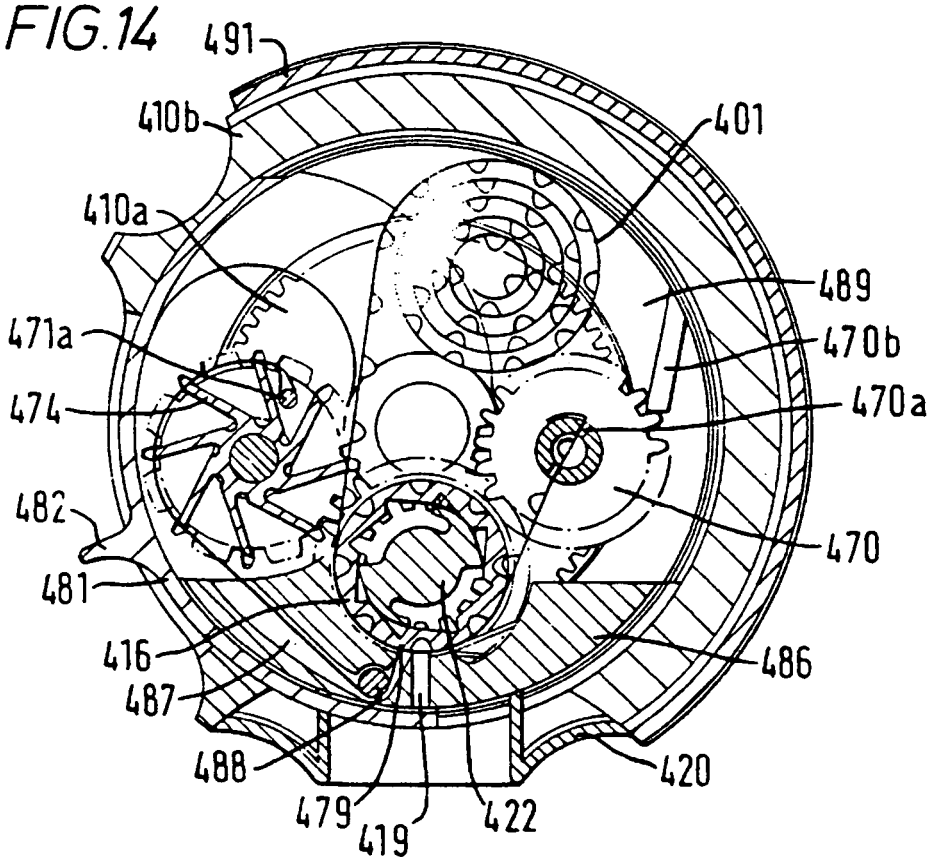


FIG.15

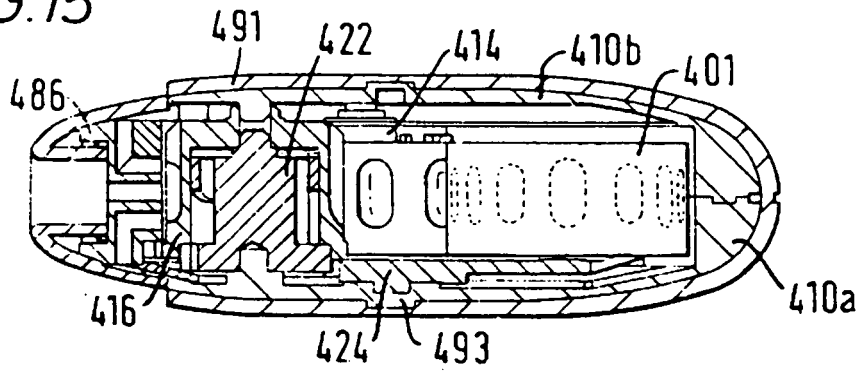


FIG.16

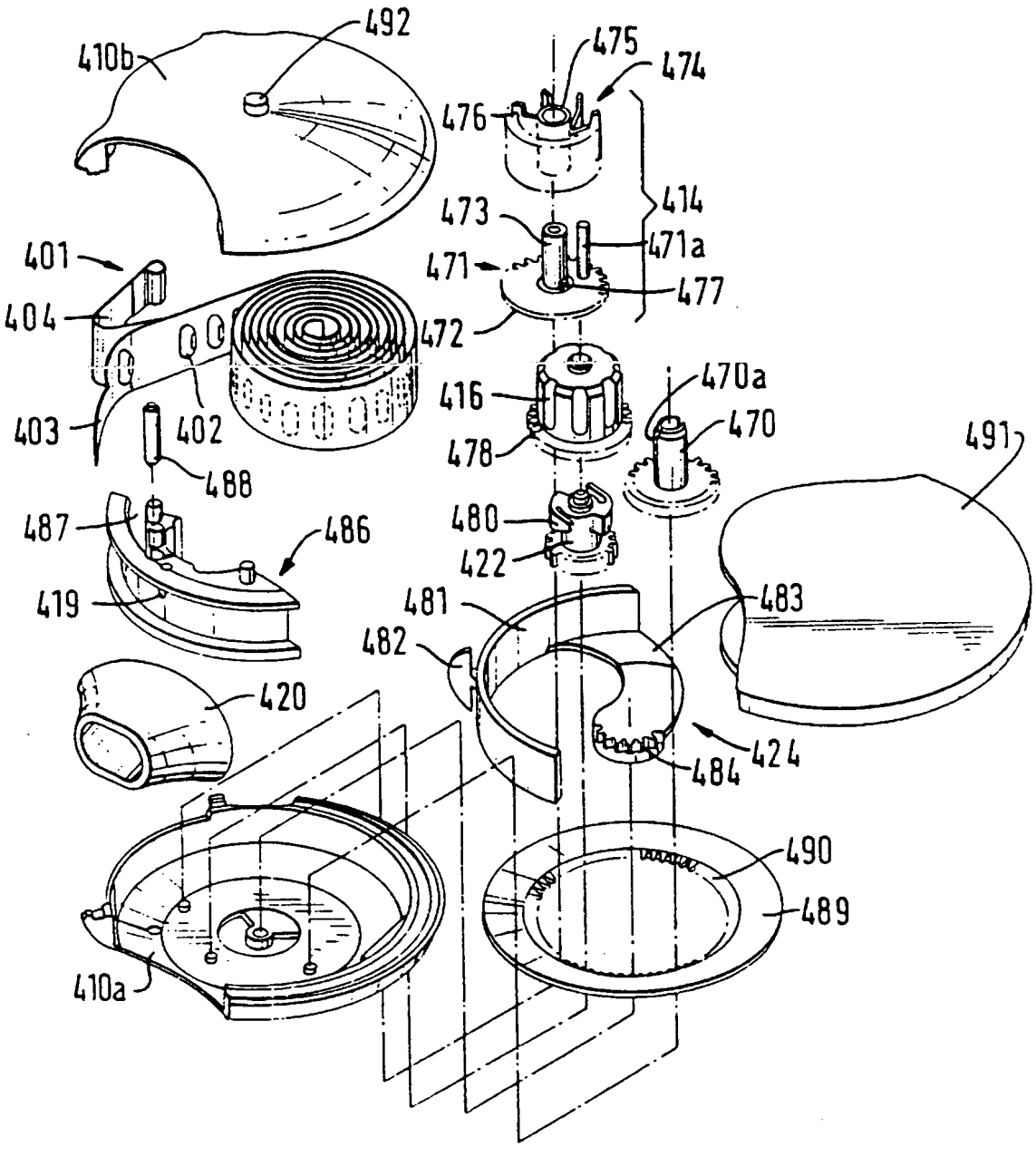

492
410b
475
474
476
414
473
471a
401
471
477
404
472
470a
416
470
403
402
478
491
488
480
487
486
422
419
481
483
482
420
424
484
490
489
410a

FIG. 16a

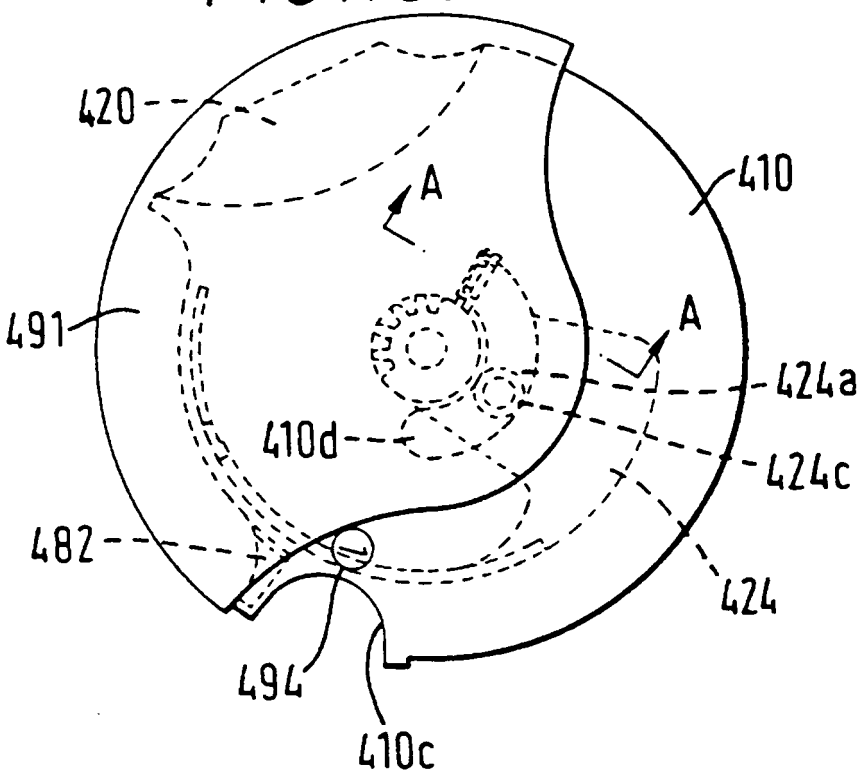


FIG. 16b

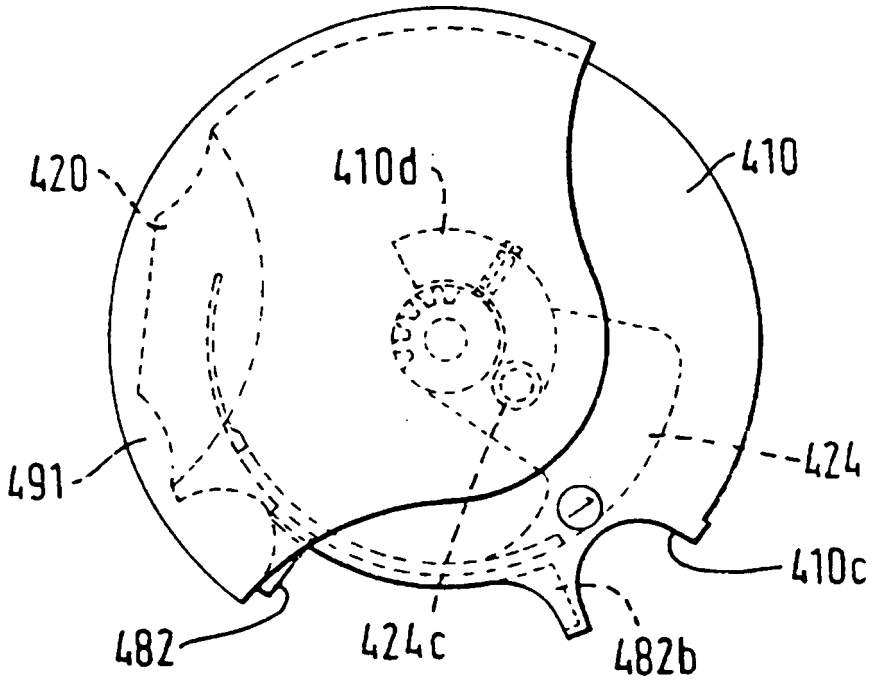


FIG. 16c

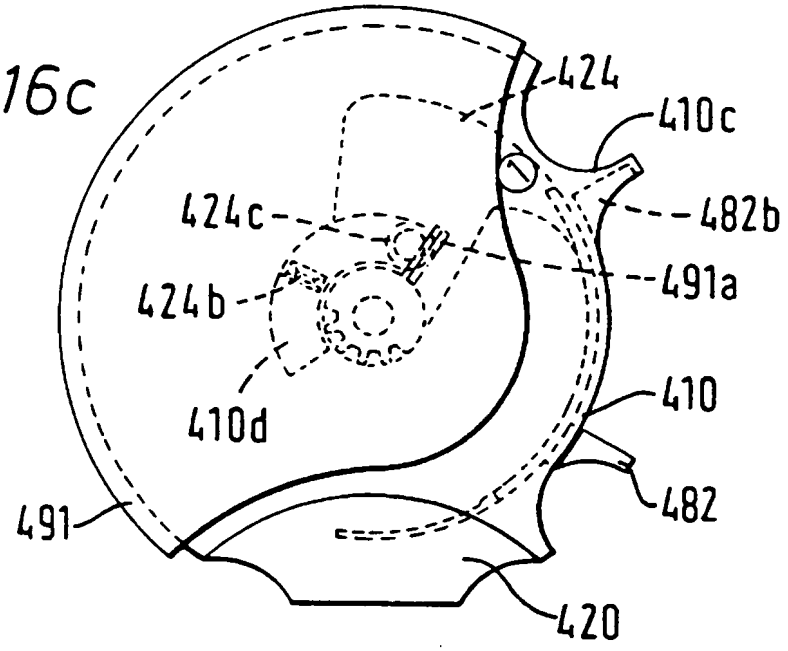


FIG. 16d

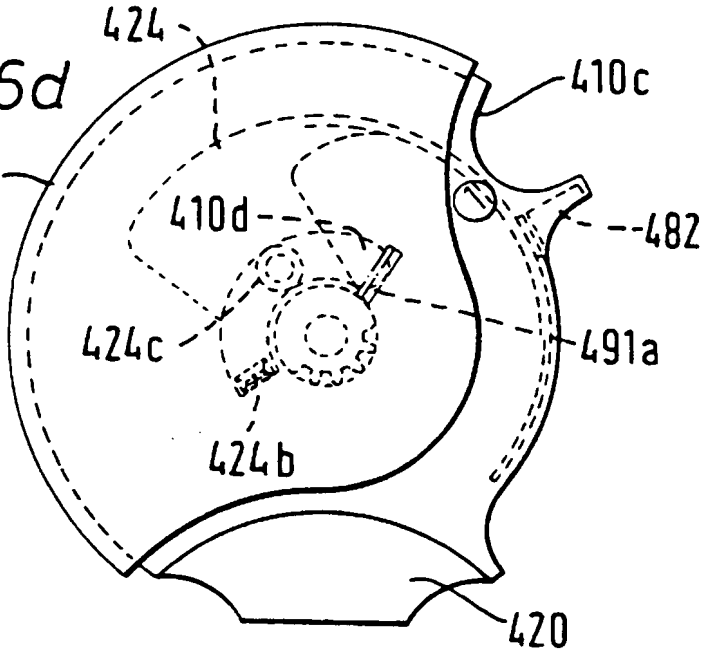


FIG. 16e

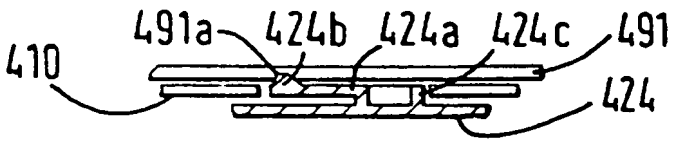


FIG. 17

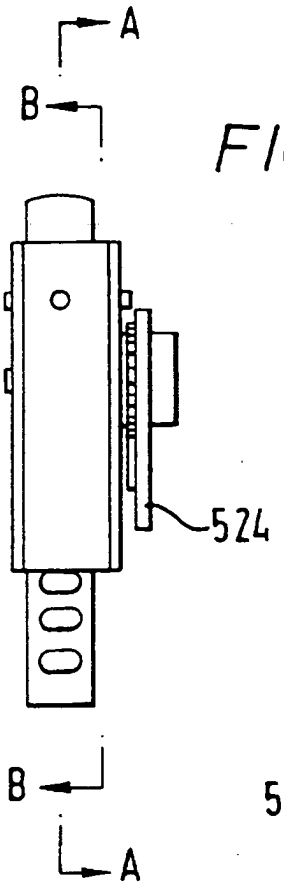


FIG. 18

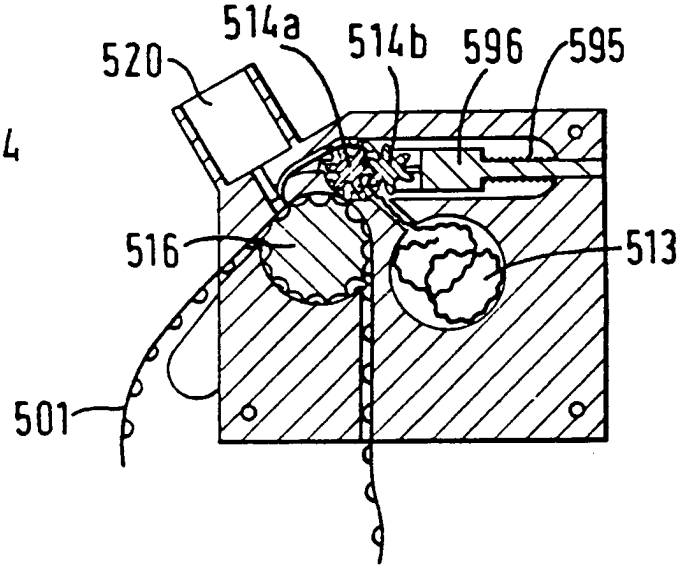
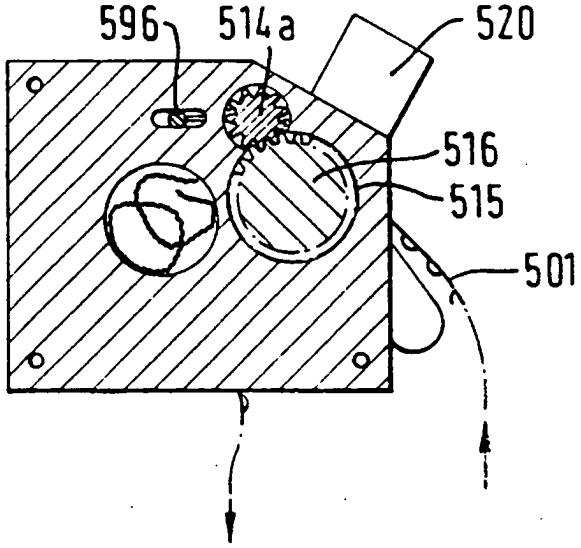


FIG. 19



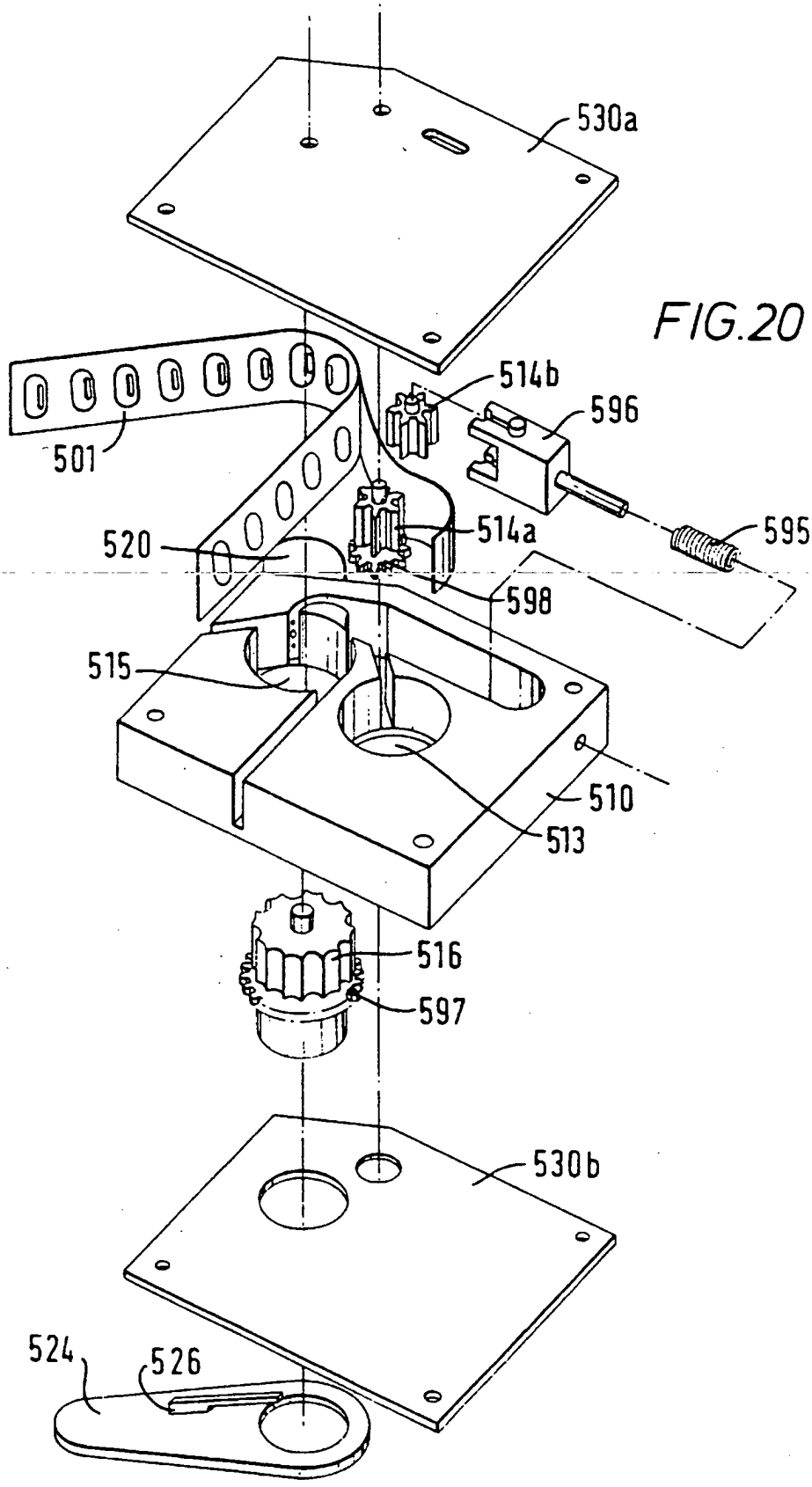

530a
514b
596
501
595
520
514a
598
515
510
513
516
597
530b
524
526

FIG.20

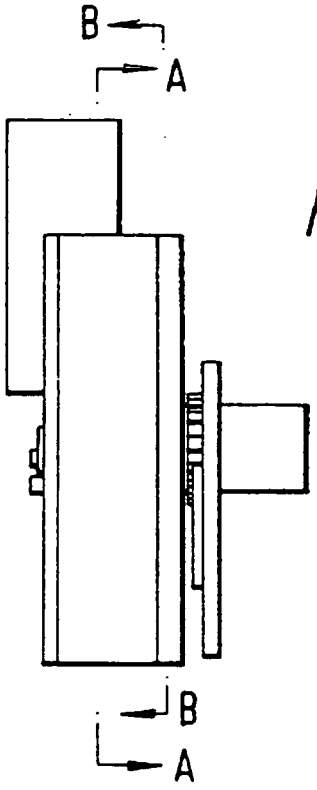


FIG. 21

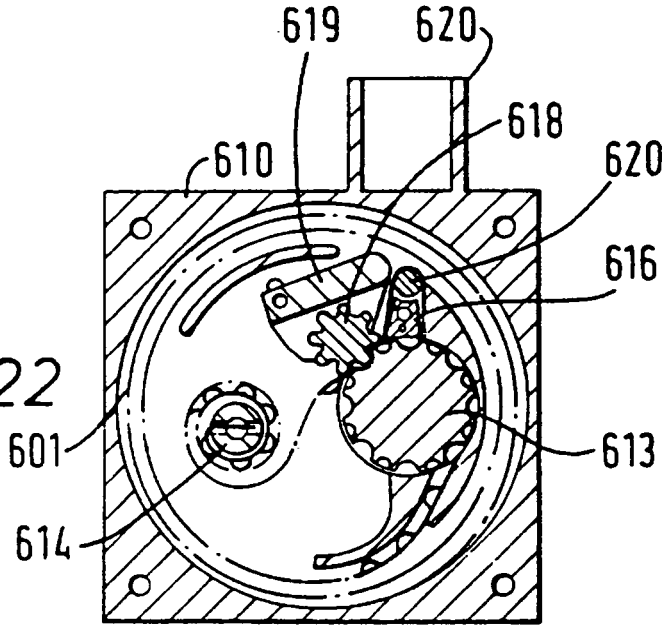


FIG. 22

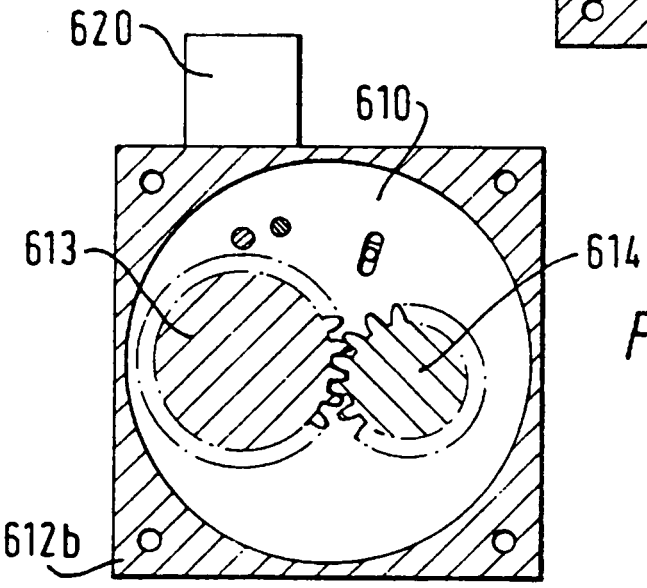


FIG. 23

FIG. 24

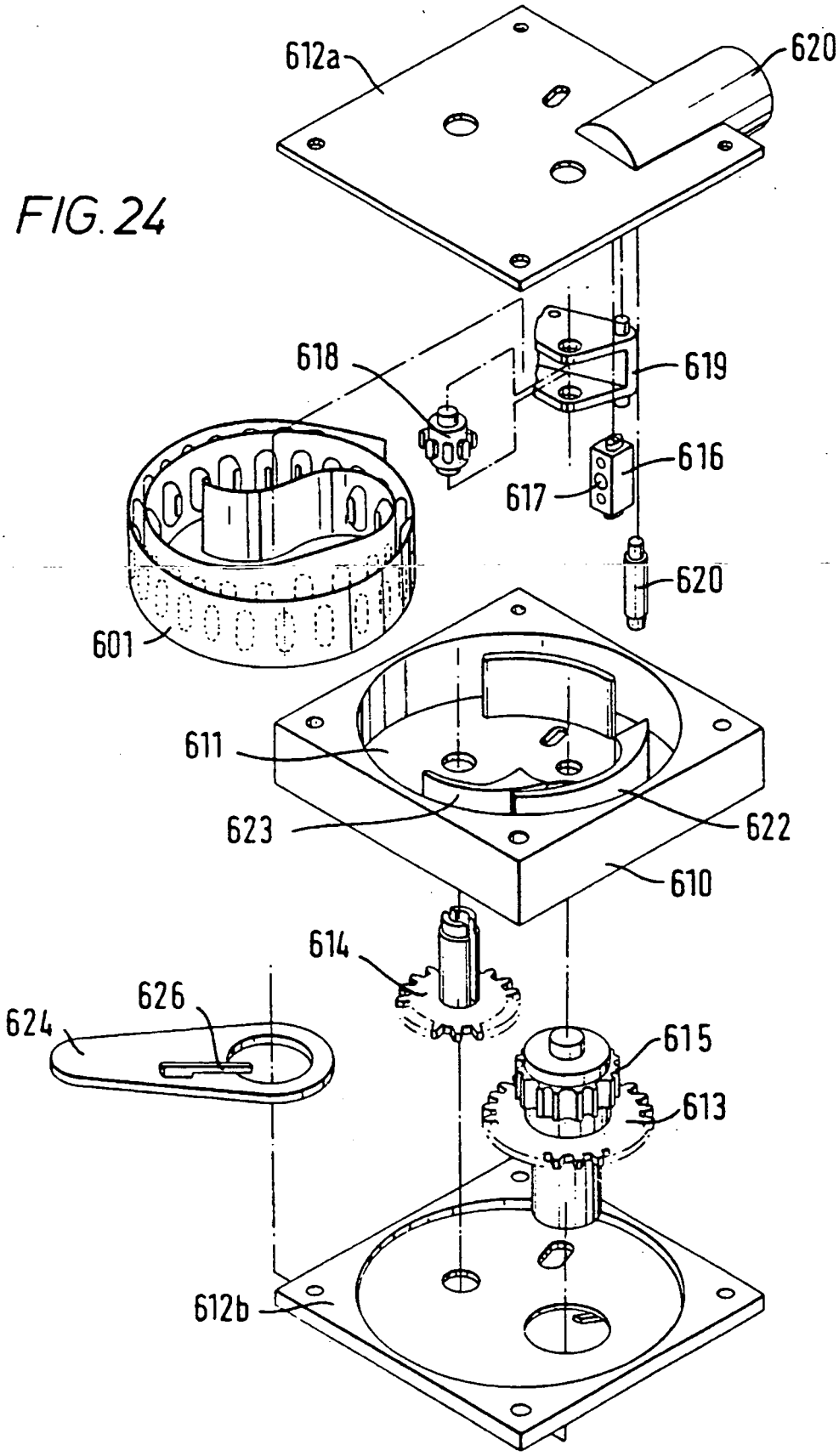

612a
620
618
619
616
617
620
601
611
623
622
610
614
626
624
615
613
612b

FIG. 25

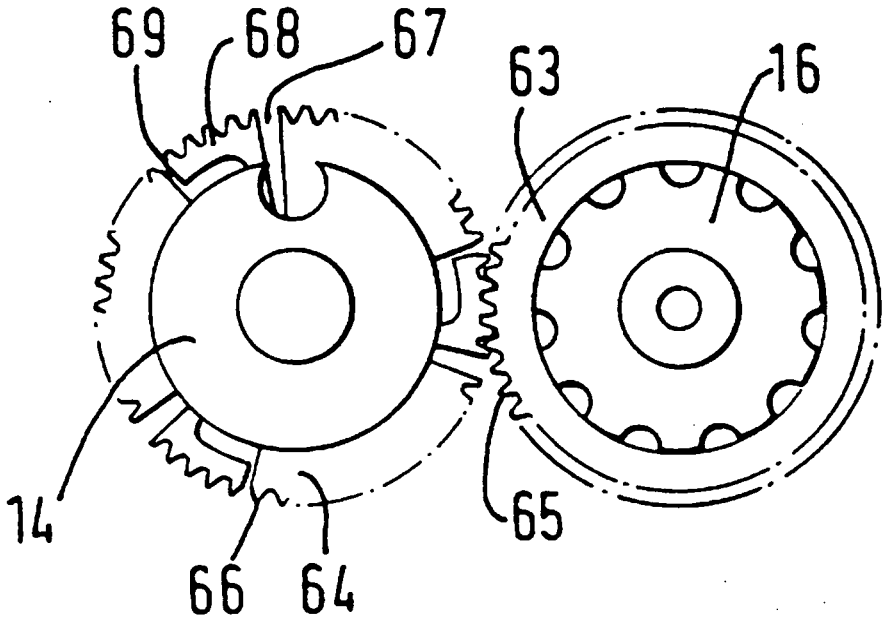


FIG. 26

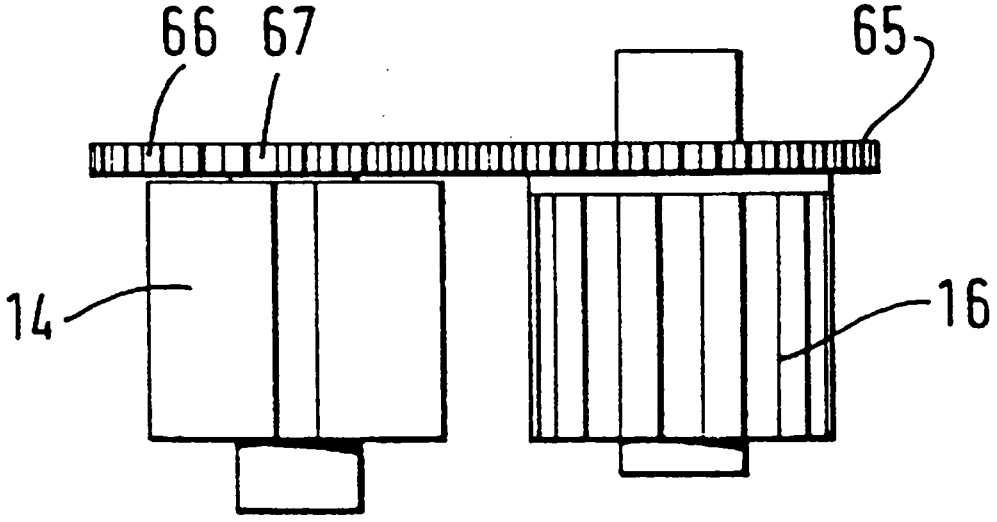


FIG. 27

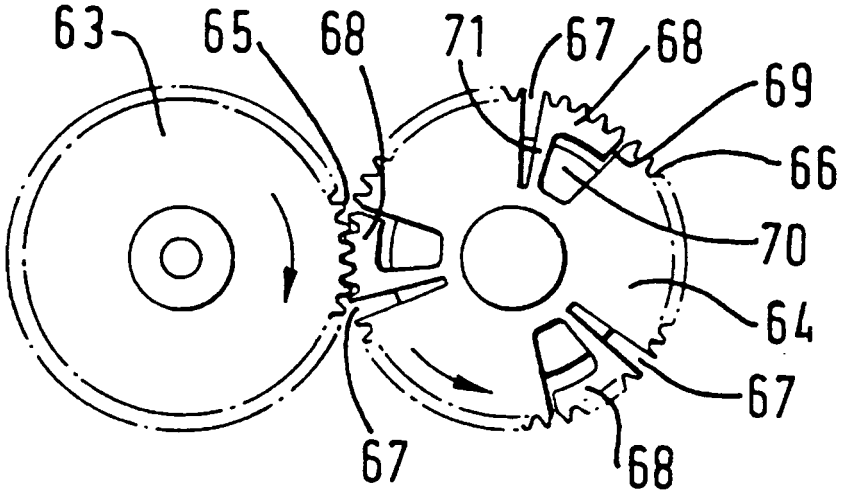


FIG. 28

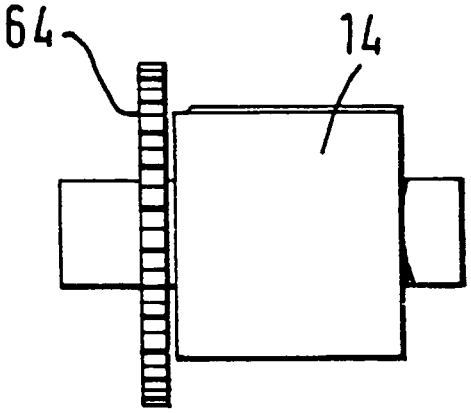


FIG. 29

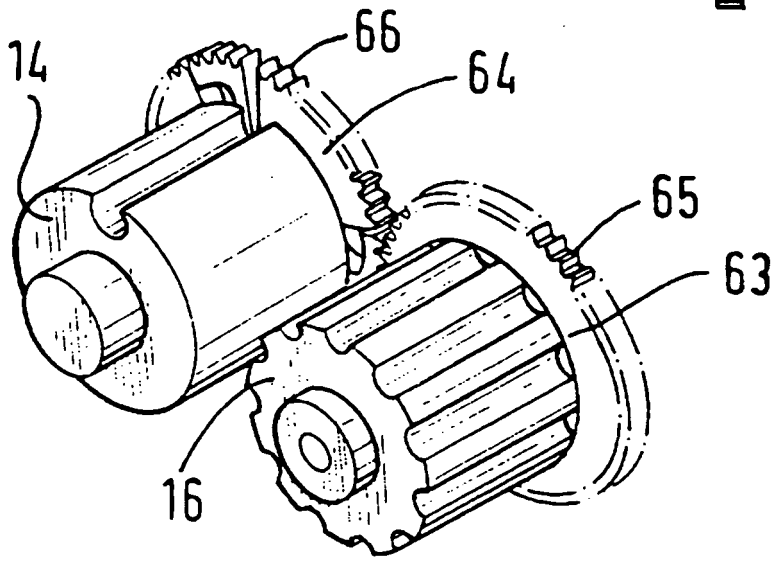


FIG. 31

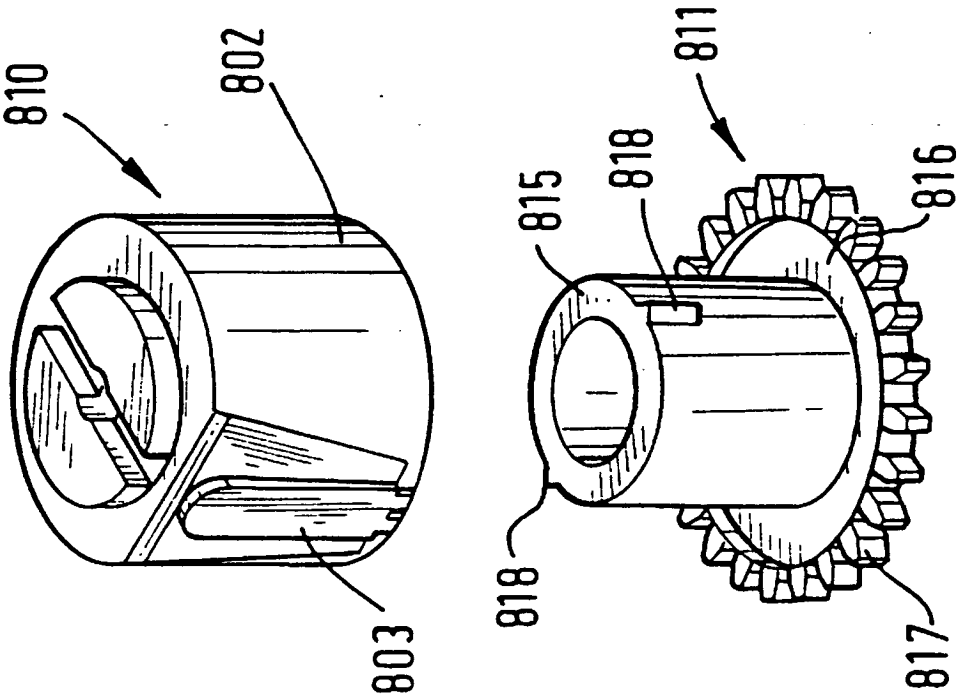

810
802
803
811
818
815
816
818
817

FIG. 30

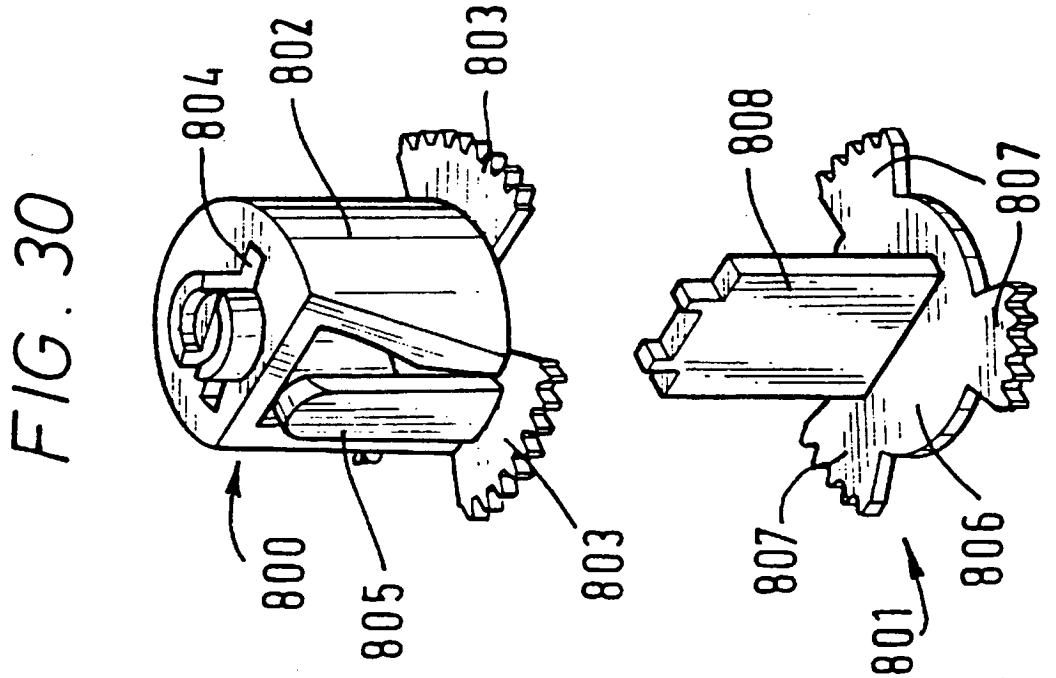

804
802
803
800
805
803
808
807
807
806
801

FIG. 31a

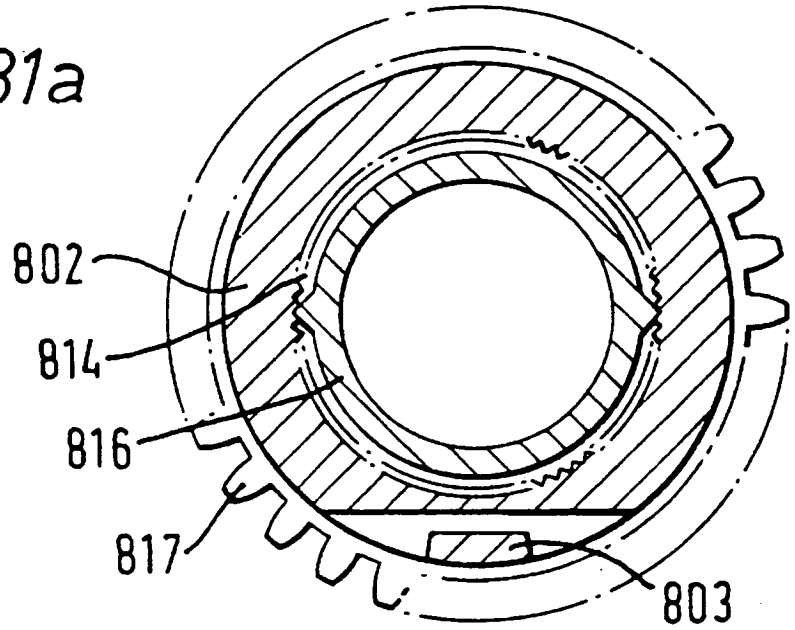


FIG. 35

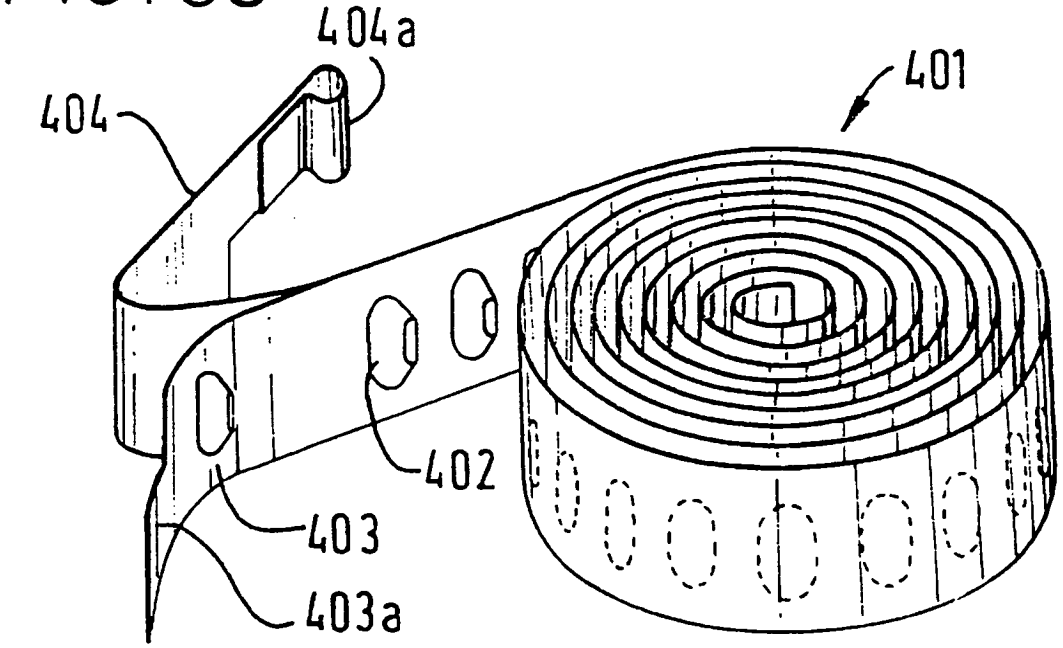


FIG. 32

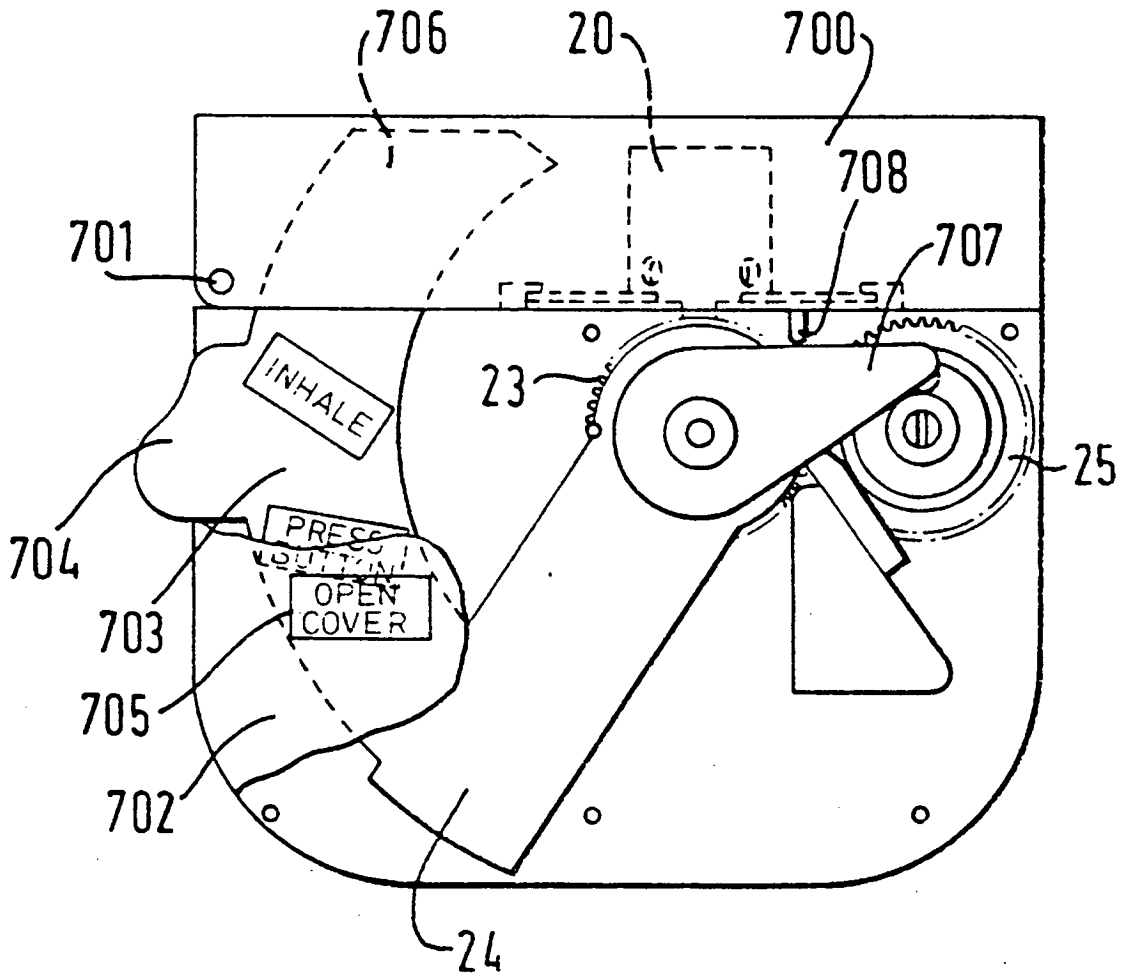

706
20
700
708
701
707
INHALE
23
25
704
PRESS
OPEN
COVER
703
705
702
24

FIG. 33

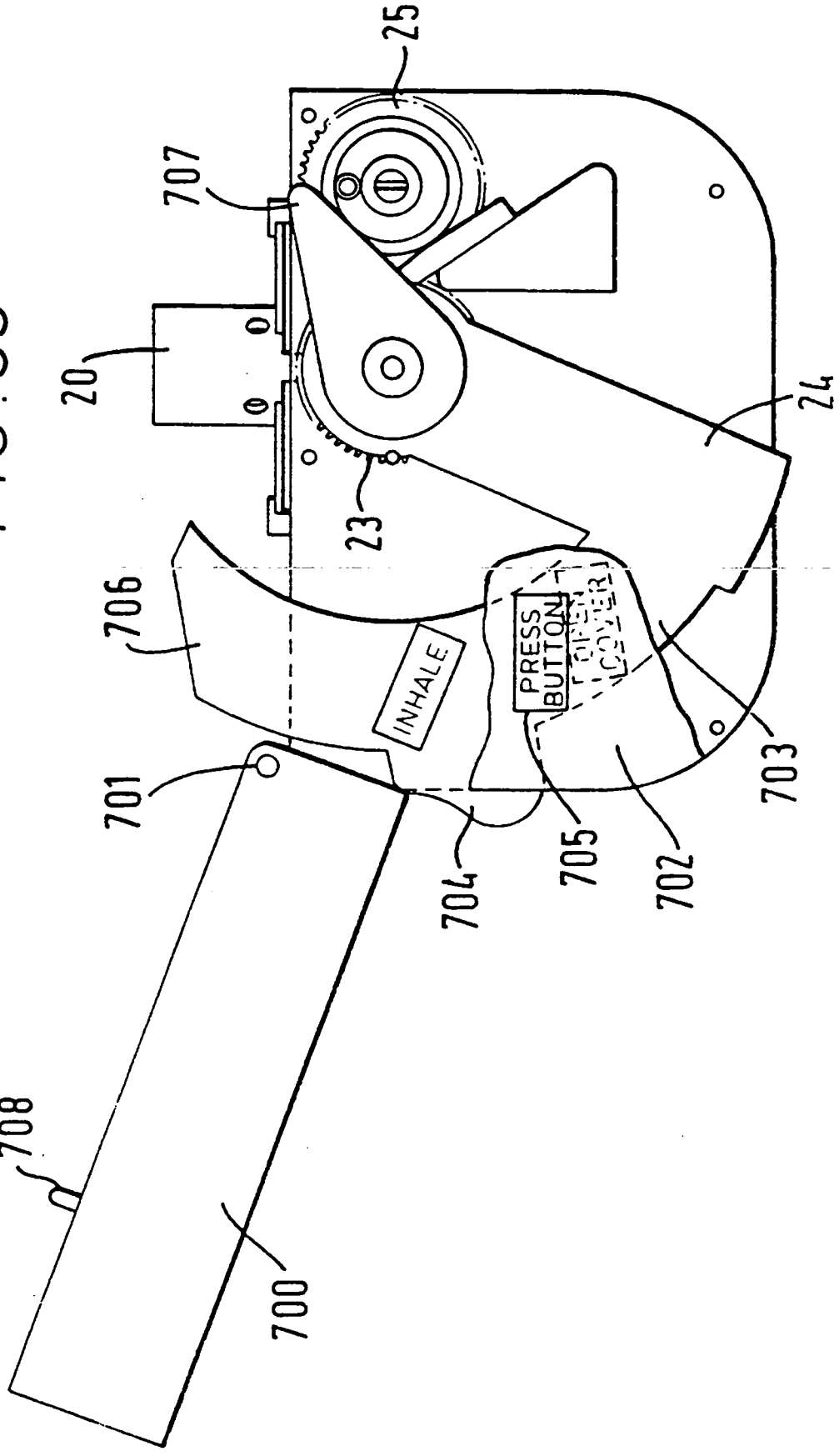
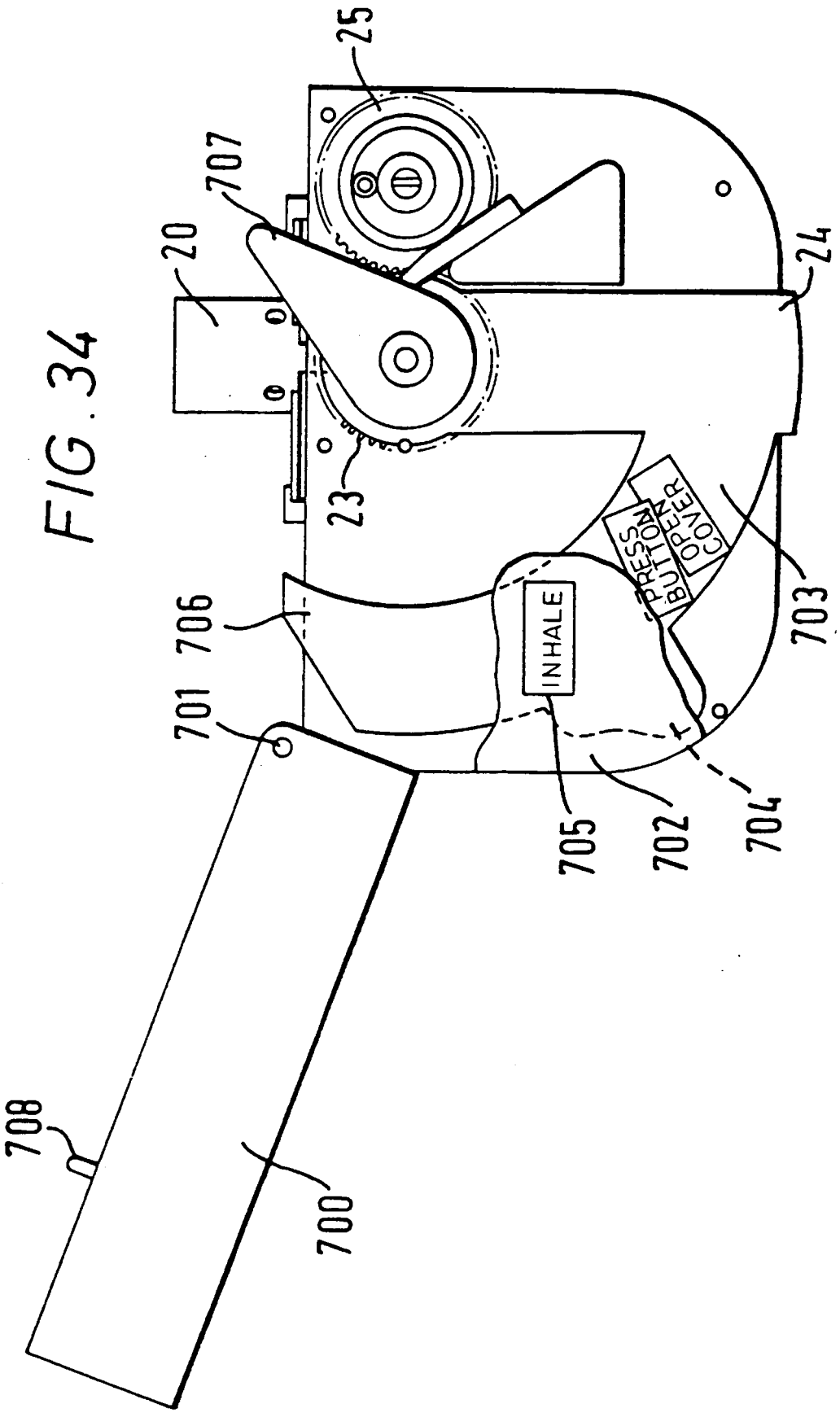

25
707
20
24
23
706
INHALE
PRESS BUTTON
703
701
704
705
702
708
700

FIG. 34


25
707
20
24
23
PRESS BUTTON TO OPEN COVER
703
706
INHALE
701
705
702
704
708
700

INHALATION DEVICE

This is a continuation, of application Ser. No. 8/175,174, filed Dec. 28, 1993, now abandoned which is a continuation of 7/633,145, filed Mar. 1, 1991 now abandoned.

FIELD AND BACKGROUND OF THE INVENTION

This invention relates to an inhalation device by means of which a user can inhale medicament in the form of a powder.

Inhalation devices are known for use with blister packs in which the medicament is held in powder form in the blisters thereof. Such devices include a puncturing member which punctures each blister in turn, thus enabling the medicament to be inhaled therefrom. It is an object of the present invention to provide an inhalation device the design of which has the potential, if desired, to handle a medicament pack having a large number of discrete unit doses, without the device becoming unacceptably large.

BRIEF SUMMARY OF THE INVENTION

According to the present invention there is provided an inhalation device for use with a medicament pack in which at least one container for medicament in powder form is defined between two members peelably secured to one another, the device comprising means defining an opening station for the said at least one container; means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale medicament in powder form from the opened container.

Preferably the medicament pack is formed from two elongate sheets which define a plurality of medicament containers spaced along the length thereof, means being provided for indexing each container in turn to the opening station.

The invention also provides a medicament pack for use in an inhalation device, the pack comprising an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein inhalable medicament in powder form. The strip is preferably sufficiently flexible to be wound into a roll.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a rear view of a first embodiment of the invention;

FIG. **2** is an axonometric exploded view of the components of the embodiment of FIG. **1**;

FIGS. **3***a*, **3***b* and **3***c* are an axonometric view, a longitudinal section and an end view (partly broken away) showing a clutch used in the embodiment of FIGS. **1** and **2**;

FIGS. **4***a* and **4***b* are an axial section and cross-section respectively, on a larger scale than FIGS. **1** and **2**, of a mouthpiece which may be used in the first embodiment (or in some other embodiment);

FIG. **5** is a front view of a second embodiment, with a cover thereof removed to show the interior;

FIG. **6** is a rear view of the second embodiment, but showing the interior thereof

FIG. **7** is an axonometric front view of the second embodiment;

FIG. **8** is an axonometric rear view of the second embodiment;

FIG. **9** is an axonometric exploded view of the second embodiment;

FIG. **10** is a front view of a third embodiment, showing the interior structure thereof;

FIG. **11** is an axial view, on a larger scale, showing the mouthpiece of the third embodiment;

FIG. **12** is a view from below of the third embodiment;

FIGS. **13** to **16** show a fourth embodiment of the invention, FIG. **13** being an underplan view, FIG. **14** a section on line A—A in FIG. **13**, FIG. **15** a section on line B—B in FIG. **13**, and FIG. **16** an exploded view on a smaller scale;

FIGS. **16***a* to **16***d* show the fourth embodiment in successive stages of operation, and FIG. **16***e* is a section taken on line A—A in FIG. **16***a*;

FIGS. **17** to **20** show a fifth embodiment of the invention, FIG. **17** being an end view, FIG. **18** a section on line A—A in FIG. **17**, FIG. **19** a section on line B—B in FIG. **17**, and FIG. **20** an exploded view;

FIGS. **21** to **24** show a sixth embodiment of the invention, FIG. **21** being an end view, FIG. **22** a section on line A—A in FIG. **21**, FIG. **23** a section on line B—B in FIG. **21**, and FIG. **24** an exploded view;

FIGS. **25** to **29** show a modified clutch which may be used in those embodiments of the invention which require it, and are, respectively, a front view, a top view, a back view, a left side view and an axonometric view;

FIG. **30** is an exploded perspective view showing a further embodiment of clutch which may be used;

FIG. **31** is an exploded perspective view of yet another embodiment of clutch which may be used;

FIG. **31***a* is transverse section through the clutch shown in FIG. **31**;

FIGS. **32** to **34** show successive positions of operation of another embodiment of the invention, in rear view; and

FIG. **35** is a perspective view on a larger scale showing an embodiment of medicament pack according to the invention.

DESCRIPTION OF PREFERRED EMBODIMENTS

Referring now to FIGS. **1**, **2** and **3***a* to **3***c*, these show an inhalation device in which is mounted a flexible strip **1** defining a plurality of pockets **2** each of which contains a dose of medicament which can be inhaled, in the form of a powder. The strip **1** comprises a base sheet **3** in which blisters are formed to define the pockets **2**, and a lid sheet **4** which is hermetically sealed to the base sheet **3** except in the region of the blisters, in such a manner that the lid sheet and the base sheet can be peeled apart. The sheets are sealed to one another over their whole width except for leading end portions thereof where they are preferably not sealed to one another at all. The lid and base sheets are each preferably formed of a plastics/aluminium laminate, and the lid and base sheets are preferably adhered to one another by heat sealing. By way of example, the lid material may be a laminate consisting of 50 gsm bleach kraftpaper/12 micron polyester (PETP) film/20 micron soft temper aluminium foil/9 gsm vinylic peelable heat seal lacquer (sealable to PVC), and the base material may be a laminate consisting of 100 micron PVC/45 micron soft temper aluminium foil/25 micron orientated polyamide. The lacquer of the lid material is sealed to the PVC layer of the base material to provide the

peelable seal between the lid and base sheets.

The strip **1** is shown as having elongate pockets which run transversely with respect to the length of the strip. This is convenient in that it enables a large number of pockets to be provided in a given strip length. The strip may, for example, be provided with sixty or one hundred pockets, but it will be understood that the strip may have any suitable number of pockets.

The inhalation device comprises a body **10** defining three storage chambers, namely a chamber **11** in which the strip **1** is initially housed and from which it is dispensed, a chamber **12** for receiving the used portion of the base sheet **3**, and a chamber **13** within which the used portion of the lid sheet can be wound up on a wheel **14**. The chambers **11** and **12** contain respective curved leaf springs **28** and **29**, the purpose of which is described below. The body defines a further chamber **15** which houses an index wheel **16**. This has a plurality of grooves **17** extending parallel to the axis of the wheel **16**. The grooves are spaced at a pitch which is equal to the distance between the centre lines of adjacent pockets **2**. The chambers **11**, **12**, **13** and **15** are closed by a lid **30**. The chamber **15** communicates with the chambers **11**, **12** and **13** via passages **31**, **33** and **32** respectively.

The chamber **15** communicates via a slit **18** which, in turn, extends upwardly within a mouthpiece **20**. The slot **18** also communicates with air inlets, as will be described below with reference to the specific mouthpiece shown in FIGS. **4***a* and **4***b*. The mouthpiece **20** is provided with additional air inlets **21** shown here in the form of a pair of circular apertures, though they may be of some other shape, as they are in Figures **4***a* and **4***b*. The primary purpose of the additional air inlets **21** is to provide additional air to the user and thus reduce the resistance to inhalation, though they may serve one or more additional purposes, as they do in FIG. **4***a* and **4***b* and as is described below with reference to those Figures.

A means is provided by which the user can rotate the index wheel and the lid wheel in steps of a predetermined size. This means comprises a ratchet wheel **22** and a gear wheel **23**, both connected to rotate in unison with the index wheel **16**, a lever **24** arranged to rotate about the same axis as the ratchet wheel **22** and gear wheel **23**, but independently thereof, and a gear wheel **25** which meshes with the gear wheel **23** and is arranged to rotate the lid wheel **14**. The lever **24** carries a pusher arm **26**, the end of which is arranged to engage the teeth of the ratchet wheel **22**. The teeth of the ratchet wheel are also engaged by a pawl **27** fixedly secured to the body **10**. For reasons which will become apparent from the description below of the operation of this embodiment, the gear wheel **25** is not connected directly to the lid wheel **14**, but is connected via a slipping clutch **50** which is housed within the lid wheel **14**. The effect of the provision of this clutch is that slipping occurs between the lid wheel and the gear wheel **25** when the force required to rotate the lid wheel exceeds a predetermined amount.

The clutch **50** comprises a disc **51** provided with radially extending serrations **52**, or other surface roughness, which is held in engagement with a similarly serrated or roughened surface **53** provided on an end face of the lid wheel **14** by a compression spring **54**. The spring **54** bears at one end against an inwardly directed surface **55** of the lid wheel and at the other end against a nut **56** threaded on a bolt **57**.

The device described above can be made so as to be reusable after the doses of medicament contained in the pockets **2** have all been dispensed. In that case, provision can be made for the user to gain access to the interior of the device, for example by removing the lid **30**, so as to insert therein a fresh strip **1**, for example in a cassette. Alternatively, however, the device may be made to be disposable once the strip **1** with which it is supplied has been used up.

In either event, when the device is first used the bulk of the strip **1** is within the chamber **11**, kept in a relatively tight reel by the leaf spring **28**, with a short portion at the leading end thereof passing out of the chamber **11** through the passage **31** to the index wheel **16**. The foremost part of the leading end of the strip is peeled apart so that the leading end of the lid sheet **4** can be secured to the lid wheel **14**, and so that the leading end of the base sheet **3** can enter the passage **33**. The end of the lid sheet **4** is held in place on the lid wheel **14** by means of a key **34** which is a force fit in a slot **35** in the wheel **14**.

A user desiring to use the device pushes the lever **24** in an anticlockwise direction, as viewed in FIG. **1**, so that the pusher arm **26** urges the ratchet wheel **22** through an angle equal to the angular distance between two adjacent teeth. This causes the ratchet wheel **16** to rotate by an angular amount equal to the pitch of the groove **17** thereof and thus equal to the distance between two adjacent pockets **2** in the strip **1**. This brings a pocket **2** opposite the slot **18** in the body **10**. Since the ratchet wheel **22** and gear wheel **23** move in unison, and since the gear wheel **25** meshes with the gear wheel **23**, movement of the lever **24** also causes the lid wheel **14** to rotate. This peels a sufficient portion of the lid sheet **4** away from the base sheet **3** to expose the contents of the pocket **2** which is being brought into alignment with the slot **18**.

When the user inhales through the mouthpiece **20** the flow of air which this produces entrains powder from the opened pocket, so that the powder is inhaled by the user. One way in which this can occur is explained in more detail below with reference to the embodiment of mouthpiece shown in FIGS. **4***a* and **4***b*. Each time the above procedure is repeated a further length of lid sheet is wrapped around the lid wheel **14** and a further length of base sheet enters chamber **12** through passage **33**. The leaf spring **29** therein ensures that the base sheet is coiled up and does not snag on the wall of the chamber **12**.

One effect of winding up the lid sheet on the lid wheel **14** is that the external diameter of the wheel plus the sheet wound thereon gradually increases. Were it not for the use of a slipping clutch to connect the gear wheel **25** to the lid wheel **14** this would have the result that successive operations of the lever **24** would try to cause a progressively longer length of lid sheet to be wound on to the lid wheel. The slipping clutch **50**, however, avoids this effect, the clutch slipping each time by an amount sufficient to ensure that for every operation of the lever the amount of lid sheet wound on is precisely equal to the pitch of the pockets **2**.

FIGS. **4***a* and **4***b* show a portion of the index wheel **16** with a pocket **2** therein, in conjunction with a mouthpiece which differs slightly from the mouthpiece **20** shown in FIGS. **1** to **3**, and which is denoted by reference numeral **120**. The mouthpiece **120** has air inlets **140**, to which reference in general terms has already been made in connection with FIGS. **1** to **3**, and a central powder outlet **119**, one end of which is open to the pocket **2** and the other end of which opens into the interior of the mouthpiece **120**.

When a user inhales through the mouthpiece **120** this causes air to flow in through the inlets **140** and thence through the pocket **2**, into the powder outlet **119**, and out through the mouthpiece **120**. By thus directing the flow of air through the pocket **2**, efficient entrainment of powder in

the airflow is achieved, with consequent efficient emptying of the pocket. The mouthpiece **120** is provided with additional air inlets **121**, shown here by way of example as being four in number, which open tangentially into the mouthpiece. When the user inhales air is drawn into the mouthpiece not only through the air inlets **140** but also through the air inlets **121**, and the air entering through the inlets **121** produces a swirling airflow which helps to distribute powder effectively within the airflow and reduce the extent to which powder is deposited on the inside of the mouthpiece. This also helps to break up any aggregates of powder which may be present in the blister.

An alternative clutch arrangement is shown in FIGS. **25** to **29**. In this, the index wheel **16** and the lid wheel **14** have respective toothed gear wheels **63** and **64** secured to them for rotation therewith. The direction of rotation is indicated by arrows in FIG. **27**.

Gear wheel **63** has a toothed surface **65**, with the teeth being provided continuously all the way round the surface **65** and at a constant pitch. By contrast, the gear wheel **64** has a toothed surface **66** from which some teeth are missing by virtue of the provision of radially extending slots **67**. The circumferential width of each slot at the surface **66** is equal to one tooth pitch. The drawings show three such slots, but it should be understood that there could instead be one slot, two slots, or more than three slots. To one side of each of the slots **67**, in fact upstream of each slot as considered in the direction of rotation of the gear wheel **64**, a toothed section **68** is defined between the slot **67**, and a narrow slit **69**. The radially inner end of each slit **69** communicates with an aperture **70**, so that each toothed portion **68** is connected to the remainder of the gear wheel **64** only by an arm **71**. The gear wheel **64**, or at least those portions thereof which provide the arms **71**, is made of a material which permits the toothed portions **68** to flex resiliently back and forth in a circumferential direction. The rest position of the portions **68** is as shown in the drawings, but when a force is applied to a portion **68** in the direction of rotation of the gear wheel **64**, the portion **68** can move so as to close the gap **67** at the radially outer end. This has the effect that a tooth is then "missing" not at the end of the slot **67** but at the end of the slit **69**.

When the circumferential force applied by the gear wheel **63** to the gear wheel **64** is below a predetermined level the toothed portions **68** remain in their rest positions and the gear wheel **64** behaves just as if it had a continuous toothed surface like that of gear wheel **63**. However, if the load exceeds a predetermined value, each time a toothed section **68** meshes with the gear wheel **63** it is moved circumferentially to close up the slot **67** at its outer end and open the slit **69**. This movement of the toothed section **68** by a distance equal to the tooth pitch has the effect of producing slippage of the gear wheel **64** with respect to the gear wheel **69** equal to one tooth pitch. In this way, the illustrated arrangement is able to permit a total slippage of the gear wheels with respect to one another by a maximum of a distance equal to three times the tooth pitch per revolution, and hence a corresponding slippage of the lid wheel and index wheel with respect to one another. As will be appreciated, providing more or fewer toothed sections than the three illustrated will permit more or less than this maximum slippage.

A second embodiment of the inhalation device according to the invention is shown in FIGS. **5** to **9**. This is intended for use with a strip **201**, similar to the strip **1** used in the first embodiment except as regards the spacing of the pockets (for which see below). In many respects the second embodiment resembles the first embodiment, and components in the second embodiment which correspond in general terms to particular components in the first embodiment are denoted by the same reference numerals, but with the addition of **200**. The main difference between the first embodiment and the second embodiment is that in the latter there is no index wheel corresponding to the index wheel **16** of the first embodiment. Instead, indexing of the strip **1**, to ensure that each operation of the lever advances the strip by an amount equal to the pitch of the pockets, is achieved by a resiliently flexible arm **250** terminating in a tooth **252** which engages between adjacent pockets. Each time the lever **224** is operated the arm **250** is resiliently depressed as a pocket slides past the tooth **252** thereof, and the tooth then springs back into engagement with the strip to the rear of the pocket which has just passed it.

It will be appreciated that, as in the case of the first embodiment, the diameter of the lid wheel **214** with the lid sheet thereon gradually increases during operation. Since a slipping clutch cannot be used in this embodiment the effect just described is compensated by having the spacing of the pockets **2** gradually increasing towards the rear end of the strip.

One other difference which will be noted between the first and second embodiments, is that in the latter the chambers **211** and **212** form a single composite chamber, unlike the separate chambers **11** and **12** in the first embodiment. However, this need not be so, and the first embodiment could use a single composite chamber and the second embodiment could use separate chambers.

FIGS. **10** to **12** show a third embodiment. In many respects this resembles the second embodiment, and components in the third embodiment which correspond in general terms to components in the second embodiment are denoted by the same reference numerals but with the addition of a further 100.

One difference which will be observed between the second and third embodiments is that in place of the lid wheel **114** a pair of wheels **314***a* and **314***b* are employed, with the lid sheet being gripped in the nip between the wheels **314***a* and **314***b*, which act as a mangle. These wheels are knurled or otherwise roughened to improve the grip between the wheels and the lid sheet. The used lid sheet is not wound up but is fed into a chamber **313**, so that no problem arises, as it does in the first two embodiments, with the lid wheel attempting to wind up progressively longer lengths of lid as operation of the device continues.

FIG. **11** shows the mouthpiece to be of a somewhat different design to that shown in FIGS. **4***a* and **4***b*. The mouthpiece is shown as having a single air inlet **340** in place of the pair of air inlets **140**, and the powder outlet **119** of FIGS. **4***a* and **4***b* is replaced by a mouthpiece portion **319** of reduced width. It should be understood, however, that the device shown in FIGS. **10** to **12** could be modified so as to incorporate a mouthpiece more closely resembling FIGS. **4***a* and **4***b*.

FIG. **10** shows the device as being provided with a hinged cover **360**, and such cover could be provided for either of the first two embodiments. FIG. **12** shows the device as having a window **370** through which indicia on the strip can be viewed. By printing the strip with numbers or other indicia which correlate with the number of pockets from which powder has been dispensed, or alternatively is to be dispensed, the user is provided with an indication of how many doses have been used or, alternatively, how many doses remain. Another possibility is to use a dose counting device

driven by one of the rotating components of the inhalation device. It should be noted that similar indicia and means for viewing those indicia could be provided in all the embodiments.

FIGS. **13** to **16** show a further embodiment of the invention. This is similar in the principle of its operation to the first embodiment, and components in the fourth embodiment which correspond in general terms to components in the first embodiment are denoted by the same reference numerals but with the addition of **400**.

As in the first embodiment, the device receives a flexible strip, here denoted as **401**, comprising a base sheet **403** in which pockets **402** are defined and a lid sheet **404**. The strip **401**, is shown most clearly in FIG. **35**. The lid sheet **404** has a loop **404***a* formed at the leading end thereof for engagement over a post **471***a* extending upwardly from a toothed wheel **471** (described below). The base sheet has a lead portion **403***a* of reduced width for engagement in a slot **470***a* formed in the base winding wheel **470** (described below). The leading end portions of the base sheet and lid sheet are not sealed together, as can be seen in FIG. **35**.

The body **410** comprises a base **410***a* and a top **410***b* both of generally circular shape. When the device is assembled the base and top are snap-fitted together. The body defines a single internal chamber within which the strip **401** is housed and within which are also housed a wheel **414** for winding up the used portion of the lid sheet **404**, a base winding wheel **470** and an index wheel **416**. The index wheel **416** is hollow and an index ratchet wheel **422** is housed within it. All the wheels just mentioned are mounted in the chamber defined by the body, for rotational movement with respect thereto. A pawl **470***b* is attached to the body **410** and engages the teeth of the base winding wheel **470** to prevent the wheel moving anticlockwise, thus ensuring that the strip **401** can only proceed forwards through the device.

The lid winding wheel **414** is formed in two parts, namely a toothed wheel **471** having teeth **472** and a shaft **473**, and a collapsible wheel **474** having a hollow central shaft **475** and a plurality of resilient arms **476**, for example, as shown, eight such arms, extending from the central shaft **475** each at an angle to a radius. The toothed wheel **471** has a lug **477** which engages in a corresponding notch in the shaft **475** so that the wheels **471** and **474** rotate in unison.

The hollow index wheel **416** has external teeth **478** which mesh with the teeth of the base winding wheel **470** and the teeth of the wheel **471**. Ratchet teeth **479** are formed on the internal walls of the index wheel **416**, and the index ratchet wheel **422** has two pawls **480** which engage the ratchet teeth **479**.

The device further comprises a lever **424** which comprises an arcuate wall **481** with a finger tab **482**, and an arm **483** which extends inwardly from the wall **481** and carries an arcuate array of teeth **484** at its distal end. The lever is pivotally mounted to the centre of the base **410***a* for movement about an axis which is at the centre of the pitch circle of the teeth **484**, the teeth **484** mesh with the teeth **485** on the index ratchet wheel **422**.

A manifold **486** provides communication between the chamber within the body **410** and a mouthpiece **420**. The manifold has a powder outlet **419** and also has a passageway **487** to allow used lid strip **404** to pass to the collapsible wheel **474**. Optionally, a roller **488** may be provided to guide the strip **404** into the passageway **487**.

A dose monitor ring **489** having teeth **490** is arranged to be rotatable within the body base **410***a*. On its lower surface this bears indicia (not visible in the drawings) which can be viewed by the user through a window **494** in the body **410**. It will be noted from FIGS. **16***a* to **16***d* that the window can be seen both when the cover **491** (see below) is closed and when it is open. The indicia indicate either exactly or approximately the number of doses left (or the number of doses used, if preferred). The ring **489** is rotated by virtue of the fact that its teeth **490** are engaged by the teeth **478** of the index wheel.

The device is provided under a cover **491** which is pivotally mounted on the body **410** by means of a lug **492** on the body top **410***b* and a corresponding lug **493** on the body base **410***a*. The cover is pivotal between an open position (shown in FIG. **14**) in which the mouthpiece is exposed and a closed position in which it is not, as is described more fully below.

In operation, the user moves the cover **491** to its open position and then presses on the finger tab **482** of the lever **424** to cause it to move as the lever pivots. This makes the index ratchet wheel **422** rotate which, via the pawls **480**, causes the index wheel **416** also to rotate. Rotation of the index wheel **416** produces rotation of both the base winding wheel **470** and the lid winding wheel **414**, thus peeling the base sheet and lid sheet apart over a distance sufficient to expose a previously unopened pocket **402** opposite the end of the powder outlet **419** in the manifold **486**. The patient can then inhale through the mouthpiece, as in the preceding embodiments.

Successive stages in the operation of the device are shown in FIGS. **16***a* to **16***d*. The device is in its closed position in FIG. **16***a*. The finger tab **482** of the lever **424** is at this stage in a recess **482***b* formed in the body **410** (seen more clearly in FIGS. **16***b* and **16***c*). The cover **419** is held stationary as the body **410** is rotated anticlockwise, a recess **410***c* being provided in the periphery of the body to enable the user to insert a finger for this purpose. The device is thus moved to the partly open position shown in FIG. **16***b*. During this process the lever **424** remains stationary with respect to the cover **491**. This is achieved by the lever being provided internally with a resilient arm **424***a* the tip **424***b* of which engages in a recess **491***a* in the cover **491**. The arm **424***a* is attached to the lever **424** via a cylindrical member **424***c*. As viewed in FIG. **16***a*, the arm **424***a* extends anticlockwise from the member **424***c* over an arc of about 90°. The cylindrical member **424***c* is guided in an arcuate slot **410***d* formed in the body **410**. The slot **410***d* extends through an arc of about 180°, and in FIG. **16***a* the member **424***c* is shown as being approximately half way along its length. In FIG. **16***b* it is shown as being at one end.

The user continues to rotate the body **410** from the position shown in FIG. **16***b* to the position shown in FIG. **16***c*. During this further rotation tip **424***b* of the arm **424***a* jumps out of the recess **491***a*. This occurs because, with the member **424***c* at one end of the slot **410***d*, movement of the body **410** carries the member **424***c* with it in an anticlockwise direction and hence compels the arm **424***a* likewise to move anticlockwise. The user then moves the lever **424** by pushing on the finger tab **482** to cause it to rotate anticlockwise through the position shown in FIG. **16***c* to the position shown in FIG. **16***d* where the finger tab **482** re-enters the recess **482***b*. The steps thus far described both expose the mouthpiece **420** and open a fresh blister. The device is therefore now ready for the user to inhale.

After use, the body **410** is rotated clockwise, the lever **424** moving in unison with the body, to bring the device back to the position of FIG. **16***a*.

It will be noted that the collapsible wheel **474** in effect assumes the function of the clutch in the first embodiment.

As more lid sheet is wound onto the wheel **474** the arms **476** gradually flex inwardly, and the effect is to keep the external diameter of the reel of wound up lid sheet substantially constant, while the internal diameter thereof gradually decreases.

Instead of the wheel **414** with its collapsible wheel **474** it is possible to use the alternative structure shown in FIG. **30** or that shown in FIGS. **31** and **31***a*. The principle of operation of the structure shown in FIG. **30** is very similar to that of the clutch arrangement shown in FIGS. **25** to **29**. The structure of FIG. **30** comprises two components **800** and **801**. The component **800** comprises a generally cylindrical hollow housing **802** open at its lower end and three arcuate arrays of teeth **803**. The cylinder **802** has a slot **804** extending through the upper surface thereof, and a post **805** for receiving the leading end of the lid sheet. The component **801** comprises a disc **806** provided with three arcuate arrays of teeth **807**, and an upright member **808** extending upwardly from the disc **806**. The member **808** is formed of a material, example a plastics material, which is resilient in torsion.

The two components **800** and **801** are snap-fitted together so that the upper end of the member **808** is received in the slot **804** and cannot rotate with respect thereto. The arrays of teeth **803** and **807** are coplanar and alternate with one another. The teeth **803** and **807** mesh with the teeth **478** of the index wheel. Each array **807** is separated from one of the adjacent arrays **803** (but not from the other) by a gap equal to one tooth. Thus, there are three gaps, each of one tooth width, around the assembled arrays. Because the member **808** can flex in torsion, the disc **806** is free to move back and forth between a position in which the gaps are each on one side of a respective array **807** and a position in which the gaps are each on the other side of a respective array **807**. This has the effect of producing slippage of the structure shown in FIG. **30** with respect to the index wheel.

The structure shown in FIG. **31** is a slipping clutch. It comprises two components **810** and **811**, snap-fitted together. The component **810** comprises a generally cylindrical housing **812** open at its lower end and having a post **813** for receiving the leading end of the lid sheet. The interior of the housing **812** is provided with longitudinally extending serrations **814**, as can be seen in FIG. **31***a*. The component **811** comprises a cylinder **815** which extends upwardly from a disc **816** provided with teeth **817**. The teeth **817** mesh with the teeth **478** of the index wheel. The cylinder **815** is provided on its outer surface with a pair of pips **818** which are in interfering engagement with the serrations **814**. When the rotational force applied by the component **811** to the component **810** is below a predetermined level the components rotate together. However, the cylinder is made of a material, for example a plastics material, which can deform radially, and when the rotational force exceeds the predetermined level such deformation takes place, permitting the pips **818** to move over the serrations **814**.

Although in the embodiment of FIGS. **13** to **16**, with or without the modifications of FIGS. **30** and **31**, the base sheet is wound up as well as the lid sheet, it is not necessary for there also to be a slipping clutch or the like between the index wheel and the base winding wheel. The diameter of the base winding wheel is so chosen that initially the base sheet is wound up only very loosely, and the tightness with which the sheet is wound increases during operation but without ever reaching an unacceptable level. In theory, the base sheet could be wound up precisely via a slipping clutch or the like, with the lid sheet being only loosely wound, but in practice it is much easier to wind up the lid precisely because it is flat and because it is thinner than the base sheet.

FIGS. **17** to **20** show in diagrammatic form the main operative parts of a device which has some similarities to those shown in FIGS. **10** to **12**, i.e. it is a mangle device. However, it is to be understood that FIGS. **17** to **20** do not show a complete device, the chamber for the unused strip and the used base material being omitted. Components in this embodiment which correspond in general terms to particular components in the embodiment of FIGS. **10** to **12** are denoted by the same reference numerals, but with the addition of a further **200**.

The device of FIGS. **17** to **20** comprises a pair of wheels **514***a* and **514***b* which have meshing teeth formed thereon and which act as a mangle engaging the used lid material. This material is fed into a chamber **513**. The wheel **514***b* is an idler wheel and is urged into engagement with the wheel **514***a* by a compression spring **595** which acts on a carrier **596** which carries the wheel **514***b*. The wheel **514***a* has a ring of gear teeth **598** which mesh with teeth **597** formed on an index wheel **516** which performs the same indexing function as the index wheel **16** in the first embodiment and is rotatable in a chamber **515**. The chambers are formed in a body **510** and lids **530***a* and **530***b* are secured to opposite sides of the chamber. Inhalation is through a mouthpiece **520**. The device is operated by a lever **524** which turns the index wheel **516** via a pusher arm **526**.

The embodiment shown in FIGS. **21** to **24** is another type of mangle device, but one in which both the lid and base sheets pass through the wheels of the mangle.

The embodiment of FIGS. **21** to **24** comprises a body **610** defining a substantially circular chamber **611** and having lids **612***a* and **612***b* secured thereto. Within the chamber **611** an index wheel **613** and a base and lid winding wheel **614** are rotatably mounted, the wheels **613** and **614** having gear teeth which mesh with one another. The index wheel **613** has grooves **615**, and a lid gripper wheel **618**, rotatably carried in a carrier **619** is also mounted adjacent the grooves **615**, downstream of the manifold **616**. A roller **628** is mounted behind the manifold **616** to guide the lid sheet.

Flexible strip **601** is provided in the chamber **611**, the main part of the strip being initially coiled up around the internal wall of the chamber. The leading end of the strip passes between guide members **622** and **623** over part of the circumference of the index wheel **613**, with the powder containing pockets thereof engaged in the grooves **615**. At the point where the strip meets the manifold **616** it is peeled apart, and the lid sheet passes behind the manifold and over the roller **628** while the base sheet passes between the index wheel and the manifold. After the manifold both sheets pass between the index wheel and the lid gripper wheel **618**, and are gripped thereby. The front end of the strip is fixed in the base and lid winding wheel **614**.

In use, the strip **601** is advanced by rotating the index wheel, by means of a lever **624**, via a pusher arm **626**, which causes corresponding rotation of the base and lid winding wheel. This winds up the base and lid, initially loosely, though increasing in tightness as the operation proceeds, but without, however, the tightness ever reaching an unacceptable level. The lid and base sheets are peeled apart where the strip meets the manifold **616**, presenting a fresh pocket of powder to the powder outlet **617**. Inhalation is via a mouthpiece **620**.

FIGS. **32** to **34** show an embodiment of the invention incorporating, as a further feature, indicia which instruct the user as to the successive steps which the user is to take to operate the device. Apart from the indicia, the device is largely the same as the embodiment shown in FIGS. **1** to **3**,

and the same reference numerals are used for the corresponding components. However, there are some additional components, as will be apparent from the following description.

The device shown in FIGS. **32** to **34** has a cover **700** which is pivotally connected to the remainder of the device for pivotal movement about an axis **701**. The gear wheels **23** and **25** and the associated components are covered by a rear wall **702**. This extends over the whole of the rear of the device, but in the drawings all except a small portion thereof is shown broken away for ease of understanding. The lever **24** is provided with an arcuate extension **703**, on an edge whereof is formed a cam **704**. The extension **703** carries indicia in the form of instructions to the user, in this case the legends "OPEN COVER", "PRESS BUTTON", "INHALE". When the lever **24**, and hence the extension **703**, are in particular positions a respective one of these legends is visible through a window **705** in the rear wall **702**. The distal end of the extension **703** constitutes a button **706**. The end of the lever **24** remote from the extension **703** carries a tongue **707** pivotal therewith.

FIG. **32** shows the device in its rest position. The legend "OPEN COVER" is visible through the window **705**. If a patient now opens the cover **700** this brings the device into the position shown in FIG. **33**. It will be seen that the top rear edge of the cover has struck the cam **704** and moved the extension **703** through an angle such as to make the legend "PRESS BUTTON" visible through the window **705**. If the user now presses the button **706** this causes the lever **24** to rotate, thus opening a powder-containing container, as described in connection with FIGS. **1** to **3**. This brings the device into the position shown in FIG. **34**, in which the legend "INHALE" is visible through the window **705**. It will also be seen that in the position of FIG. **34** the tongue **707** protrudes upwardly. Accordingly, when the user, having inhaled, closes the cover, the tongue **707** is struck by a lug **708** on the underside of the cover, which pushes the lever **24**, with its extension **703**, back into the position shown in FIG. **32**, once again causing the legend "OPEN COVER" to be displayed.

The device just described not only gives the step-by-step instructions to the user, thus reducing the risk of a patient being confused, but also makes it difficult for the patient to use the device other than in the intended manner, by virtue of the fact that the button **706**, once depressed, is not again accessible until the user closes the cover and reopens it.

In the embodiments described above, reference is made to a mouthpiece. However, if the device was to be used for purposes other than oral inhalation some other outlet would be employed, e.g. a nosepiece.

We claim:

1. An inhalation device for use with a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are spaced along the length of and defined between two peelable sheets secured to each other, said inhalation device comprising:

an opening station for receiving a container of a medicament pack being used with said inhalation device;

means positioned to engage peelable sheets of a container which has been received in said opening station for peeling apart the peelable sheets, to open such a container;

an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container; and

indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device.

2. A device according to claim **1**, adapted for use where one of such peelable sheets is a base sheet having a plurality of pockets therein, and an other of such peelable sheets is a lid sheet, each pocket and an adjacent part of such a lid sheet defining a respective one of such containers, said means positioned to engage comprising driving means for pulling such a lid sheet and a base sheet apart at the opening station.

3. A device according to claim **2**, comprising indexing means engageable between adjacent pockets to cause each pocket in turn to be positioned in communication with the outlet.

4. A device according to claim **2**, comprising at least one chamber for receiving medicament pack before opening, and for receiving the base sheet and lid sheet after peeling apart.

5. A device according to claim **4**, further comprising resilient coil-formers for holding in coiled form at least one of: (i) a medicament pack being used with said inhalation device and; (ii) a base sheet of a container which has been received in said opening station.

6. A device according to claim **2**, wherein the said driving means comprises lid driving means for pulling such a lid sheet.

7. A device according to claim **6**, wherein the lid driving means comprises a pair of driving wheels which drivingly engage such a lid sheet between them.

8. A device according to claim **7**, wherein the said driving wheels are toothed wheels having interengaging teeth.

9. A device according to claim **6**, comprising a rotatable index wheel having recesses therein, the wheel being engageable with such a medicament pack so that the recesses each receive a respective pocket.

10. A device according to claim **9**, wherein the index wheel and the lid driving means are interconnected so that the rotation of one correlates with the rotation of the other.

11. A device according to claim **1**, further comprising means for operating in a plurality of steps, which comprises indicator means adapted to display to a user an instruction as to the next step once the preceding step has been taken.

12. A device according to claim **11**, wherein the indicator means comprises an indicator member which carries a plurality of legends each constituting an instruction to the user, the indicator member being movable by a given step being carried out to display the legend relating to the next step.

13. An inhalation device for opening a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are defined between an elongate base sheet and an elongate lid sheet peelably secured to each other with the base sheet having a plurality of pockets therein, said inhalation device comprising:

an opening station for receiving a container of a medicament pack being used with said inhalation device;

peeling means positioned to engage a base sheet and a lid sheet of a container which has been received in said opening station for peeling apart such a base sheet and lid sheet, to open such a container, said peeling means including lid driving means for pulling apart a lid sheet and a base sheet of a container that has been received at said opening station;

an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container; and

indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device, said indexing means including

a rotatable index wheel having recesses therein, said index wheel being engageable with a medicament pack in use with said inhalation device such that said recesses each receive a respective pocket of a base sheet of a medicament pack in use with said inhalation device, said index wheel and lid driving means being interconnected by a slipping clutch so that the rotation of one correlates with the rotation of the other.

14. A device according to claim **13**, wherein the slipping clutch comprises a first gear member which is movable with the index wheel and has a toothed surface, and a second toothed gear member which is movable with the lid driving means and has a toothed surface in meshing engagement with the toothed surface of the said first gear member, at least one of the toothed surfaces having a toothed portion which is movable back and forth with respect to the remainder of the toothed surface of which it is part.

15. A device according to claim **13**, wherein the slipping clutch comprises first clutch means movable with the index wheel and second clutch means movable with the lid driving means, one of the clutch means comprising an annular array of serrations and the other of the clutch means comprising means which grippingly engage the serrations when less than a predetermined force is applied between the two clutch means and which slip with respect to the serrations when a force equal to or greater than the predetermined force is applied.

16. An inhalation device for opening a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are defined between an elongate base sheet and an elongate lid sheet peelably secured to each other with the base sheet having a plurality of pockets therein, said inhalation device comprising:

an opening station for receiving a container of a medicament pack being used with said inhalation device;

peeling means positioned to engage a base sheet and a lid sheet of a container which has been received in said opening station for peeling apart such a base sheet and lid sheet, to open such a container, said peeling means including lid driving means for pulling apart a lid sheet and a base sheet of a container that has been received at said opening station;

an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container;

indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device, said indexing means including

a rotatable index wheel having recesses therein, said index wheel being engageable with a medicament pack in use with said inhalation device such that said recesses each receive a respective pocket of a base sheet of a medicament pack in use with said inhalation device, said index wheel and lid driving means being interconnected by a slipping clutch so that the rotation of one correlates with the rotation of the other; and

said lid driving means comprising a wheel on which a lid sheet of a medicament pack in use with said inhalation device is wound up, said wheel having a winding surface which decreases in diameter when tension in said lid sheet increases.

17. A device according to claim **16**, wherein the said wheel comprises a plurality of resiliently flexible arms each extending therefrom at an angle with respect to a radius.

18. An inhalation device for opening a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are defined between an elongate base sheet and an elongate lid sheet peelably secured to each other with the base sheet having a plurality of pockets therein, said inhalation device comprising:

an opening station

for receiving a container of a medicament pack being used with said inhalation device;

peeling means positioned to engage a base sheet and a lid sheet of a container which has been received in said opening station for peeling apart such a base sheet and lid sheet to open such a container, said peeling means including driving means for pulling apart a lid sheet and a base sheet of a container that has been received at said opening station;

an outlet positioned to be in communication with an opened container through which a user can inhale medicament in powder form from such an opened container;

indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device, said indexing means including,

means for guiding such a lid sheet and base sheet along separate paths at said opening station, said paths reuniting downstream of said opening station, said driving means being located after the point where said paths reunite and being operable to drive both a lid sheet and a base sheet.

19. A device according to claim **18**, wherein the said driving means comprises a pair of toothed wheels having interengaging teeth.

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EXHIBIT 7

Patent Term Extension Calculations

EXHIBIT 7

Patent Term Extension Calculations

IND Effective Date: **9/7/90**

9/7/90 - 12/31/90 = 116
1/01/91 - 12/31/92 = 365
1/01/92 - 12/31/92 = 366
1/01/93 - 12/31/93 = 365
1/01/94 - 12/31/94 = 365
1/01/95 - 12/31/95 = 365
1/01/96 - 6/17/96 = 169
2110 x 0.5 = 1055 days

NDA Submission Date: **6/18/96**

6/18/96 - 12/31/96 = 197
1/01/97 - 9/19/97 = 262
459 x 1 = 459 days

Patent Issue Date: **1/7/97**

1/7/97 - 9/19/97 = 246 days

NDA Approval Date: **9/19/97**

246 days of NDA Period after Patent Issued

Total Patent Term Extension: 246 days

Patent Term Extension + 20 yr GATT Expiration

Expiration 20 years from Date of First U.S. Filing: **3/1/11**

3/2/11 - 11/2/11 = 246
246 days

20 yr GATT Expiration + 246 day Patent Term Extension: **11/2/11**

14 yr Cap from NDA Approval Date

NDA Approval Date: **9/19/97**

9/19/97 + 14 yrs = 9/19/11

14 year Patent Term Cap Date: ***9/19/11***

EXHIBIT 8

Document Chronology / Due Diligence Log

for

IND 35,239

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
2	06-AUG-90	LETTER from GLAXO to FDA	INCORPORATION BY REFERENCE	UPDATE	1.001-	000
			ORIGINAL APPLICATION	DP: CONTAINER/CLOSURE SYSTEM	1.009	
			ORIGINAL APPLICATION	DP: MANUFACTURER		
			ORIGINAL APPLICATION	DP: METHOD OF MANUFACTURER		
			ORIGINAL APPLICATION	DP: SPECS/ANALYTICAL METHODS		
			ORIGINAL APPLICATION	DP: STABILITY		
			ORIGINAL APPLICATION	ENVIRON IMPACT ASSESSMENT RPT		
			ORIGINAL APPLICATION	DP: FORMULATION		
			ORIGINAL APPLICATION	INVESTIGATOR BROCHURE		
			ORIGINAL APPLICATION	CLINICAL DEVEL PROGRAM		
			ORIGINAL APPLICATION	PROTOCOL		
			ORIGINAL APPLICATION	SAFETY		
			ORIGINAL APPLICATION	PRIN-INVESTIGATOR ADD		
			ORIGINAL APPLICATION	STUDY REPORT		
			ORIGINAL APPLICATION	NON-CLINICAL GENERAL		
			ORIGINAL APPLICATION	TOXICOLOGY		
			ORIGINAL APPLICATION	TOX: ACUTE		
			ORIGINAL APPLICATION	TOX: MUTAGENICITY		
			ORIGINAL APPLICATION	ADME		

GLX SUBMITS IND FOR CLN DEVELOPMENT OF A DRY POWDER PRESENTATION FOR THE TREATMENT OF REVERSIBLE BRONCHOSPASM ASSOCIATED WITH ASTHMA.

PROTOCOL	INV#	INVESTIGATOR
SLD-201	2483	Noonan Michael

3	14-AUG-90	MEMO from GLAXO to GLAXO	REQUESTS/COMMENTS	UPDATE	2.001- 2.001	

KRAUSE CONTACTS FDA TO OBTAIN IND NUMBER AND DIVISION ASSIGNMENT FOR SALMETEROL ROTADISK IND. CLN TRIALS SHOULD NOT BE INITIATED BEFORE 07-SEP-90 UNLESS AGENCY NOTIFIES GLX THAT THEIR RVW IS COMPLETE & STUDIES MAY PROCEED PRIOR TO THIS DATE.

5	10-SEP-90	TELECON from FDA to GLAXO	STUDY HOLD	PROTOCOL	2.001- 2.001	

CSO INDICATES REVIEW TEAM HAS COMPLETED REVIEW OF IND & FEELS THAT COMPOUND IS SAFE TO ADMINISTER TO HUMANS BUT REQUESTS GLX DEFER CLINICAL TRIAL INITIATION UNTIL QUESTIONS

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		ANSWERED ABOUT STUDY DESIGN.				
6	31-OCT-90/ 29-OCT-90	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	PROTOCOL	2.001- 2.001	
		GLX CONTACTS CSO LEDET TO DETERMINE STATUS OF MEDICAL COMMENT ON STUDY HOLD FOR SLD-201. CSO SURPRISED TO LEARN THAT MEDICAL STAFF HAD NOT YET CONTACTED GLX. SINCE DVSN HAS JUST RELOCATED OFFICES, CSO SUGGESTS GLX POSTPONE FOLLOW-UP W/STAFF				
		PROTOCOL INV# INVESTIGATOR SLD-201				
7	08-NOV-90/ 07-NOV-90	TELECON from FDA to GLAXO	INFORMAL DISCUSSIONS	FDA REVIEW STATUS	2.001- 2.001	
		GLAXO INQUIRES ABOUT RMO COMMENTS ON SLD-201 & SUGGETS TELEPHONE CONFERENCE WITH RMO LEONARD BUT CSO LEDET THINKS CONTACT WOULD BE PREMATURE.				
8	26-NOV-90	TELECON from GLAXO to FDA	REQUESTS/COMMENTS REQUESTS/COMMENTS	FDA REVIEW STATUS UPDATE	2.001- 2.001	
		GLX CONTACTS CSO LEDET & INFORMS HIM GLX HAS NOT YET RECEIVED COMMENTS ON PROTOCOL SLD-201. CSO COMMENTS DELAY WOULD NOT PLEASE "CERTAIN INDIVIDIUALS" & OBTAINS NAME OF GLX CONTACT WHO WOULD DISCUSS PROTOCOL.				
		PROTOCOL INV# INVESTIGATOR SLD-201				
9	28-NOV-90	TELECON from GLAXO to FDA	INFORMAL DISCUSSIONS	FDA REVIEW STATUS	2.001- 2.001	
		GLX CONTACTS CSO TO STATE GLX HAS NOT YET RECEIVED WORD FROM RMO NICKLAS ON SLD-201. CSO ACKNOWLEDGES COMMENT.				
		PROTOCOL INV# INVESTIGATOR SLD-201				

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
10	22-JAN-91/ 11-DEC-90	TELECON from GLAXO to FDA	REQUESTS/COMMENTS REQUESTS/COMMENTS	FDA REVIEW STATUS PROTOCOL	2.001- 2.001	

GLX CONTACTS FDA TO OBTAIN COMMENTS ON SLD-201: MEDICAL REVIEWERS NOT AVAILABLE FOR COMMENT; CSO UNWILLING TO FOLLOW UP W/REVIEWERS.

PROTOCOL	INV#	INVESTIGATOR
SLD-201		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
11	22-JAN-91/ 02-JAN-91	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	PROTOCOL	2.001- 2.001	

GLX CONTACTS RMO LEONARD TO DISCUSS SLD-201; GROUP LEADER UNWILLING TO DISCUSS PROTOCOL BUT DID TAKE PHONE NUMBER FOR RETURN CALL.

PROTOCOL	INV#	INVESTIGATOR
SLD-201		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
12	28-JAN-91/ 25-JAN-91	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	FDA REVIEW STATUS	2.001- 2.001	

GLX CONTACTS GML LEONARD WHO INDICATES INTERAL PAPERS/REVIEWS FOR PROPOSED PROTOCOL MISPLACED & AGENCY LOOKING FOR THEM.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
16	08-FEB-91/ 06-FEB-91	TELECON from FDA to GLAXO	REQUESTS MEETING	UPDATE	2.001- 2.001	

DURING CONVERSATION W/CSO, GLX REMINDS CSO THAT CT STILL BEING DELAYED BECAUSE OF PENDING REQUEST FOR AGENCY COMMENT.

PROTOCOL	INV#	INVESTIGATOR
SLD-201		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
19	14-FEB-91	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	FDA REVIEW STATUS	2.001-	

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
					2.001	

GLX CONTACTS CSO LEDET FOR STATUS OF PENDING PROTOCOL REVIEW. NO NEW INFO AVAILABLE, BUT IF ANY BECOMES AVAILABLE, CSO WILL TELEPHONE WITH INFO.

20	22-FEB-91	TELECON from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS	PROTOCOL DEVICE GENERAL INFORMATION	2.001- 2.001	

CSO RELAYS RMO COMMENTS ON SLD-201: STUDY COULD PROCEED; ONLY 25 & 50MCG DOSES SHOULD BE UTILIZED BASED ON SAFETY & EFFICACY DATA PROVIDED IN PREVIOUS STUDIES; CONSIDER LONGER WASH OUT - UP TO 8 WEEKS AFTER USE OF INHALED CORTICOSTEROIDS; CLARIFY WHY 2 DIFFERENT UNIQUE "ROTADISK INHALERS" WILL BE UTILIZED.

PROTOCOL	INV#	INVESTIGATOR
SLD-201		

34	29-APR-91	FAX from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL INVESTIGATOR BROCHURE INVESTIGATIONAL DRUG LABELING	2.001- 2.001	

CSO FAXES DRAFT CMC COMMENTS FROM REVIEW OF ORIGINAL IND.

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		REFERENCE APPLICATION: IND 35239	REFERENCE ACT#: 2	SUP#/ SER#: 000	METHOD OF COMMUNICATION: LETTER from GLAXO to FDA	DOC/ACT DATE: 06-AUG-90
46	30-MAY-91/ 22-MAY-91	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	SAFETY	2.001- 2.001	
		RMO NICKLAS REQUESTS GLX PROVIDE CERTAIN "GENERAL INFORMATION" FOR FUTURE ADR SUBMISSIONS, SPECIFICALLY, TEMPORAL RELATIONSHIP BETWEEN DRUG ADMINISTRATION/ONSET OF REACTION & STATEMENT WHEN INFORMATION NOT OBTAINABLE.				
62	31-JUL-91	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY	DS: CONTAINER/CLOSURE SYSTEM	2.001- 2.001	044
			INFO AMND: CMC/MICROBIOLOGY	DS: DESCRIPTION		
			INFO AMND: CMC/MICROBIOLOGY	DS: IN-PROCESS CONTROLS		
			INFO AMND: CMC/MICROBIOLOGY	DS: MANUFACTURER		
			INFO AMND: CMC/MICROBIOLOGY	DS: METHOD OF MANUFACTURER		
			INFO AMND: CMC/MICROBIOLOGY	DS: SPECS/ANALYTICAL METHODS		
			INFO AMND: CMC/MICROBIOLOGY	DS: STABILITY		
			INFO AMND: CMC/MICROBIOLOGY	DS: SYNTHESIS		
			INCORPORATION BY REFERENCE	UPDATE		
		CMC DOCUMENTATION FOR ROTADISK IND INCORPORATED BY REFERENCE TO MDI IND: SPECIFICALLY DRUG SUBSTANCE UPDATE 1)SITES OF MFR & MICRONIZATION, 2)STABILITY & BATCH ANALYSIS DATA, 3)SYNTHESIS, & 4)ANALYTICAL METHODS & SPECIFICATIONS. File Note: Attachments filed with IND 30,905, Serial #150 and incorporated by reference to IND 35,239.				
		REFERENCE APPLICATION: IND 30905	REFERENCE ACT#: 278	SUP#/ SER#: 150	METHOD OF COMMUNICATION: LETTER from GLAXO to FDA	DOC/ACT DATE: 31-JUL-91
69	28-AUG-91	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY	C M C INCLUSIVE/GENERAL	3.001- 3.001	052
			INFO AMND: CMC/MICROBIOLOGY	DP: CONTAINER/CLOSURE SYSTEM		
			INFO AMND: CMC/MICROBIOLOGY	DP: MANUFACTURER		
			INFO AMND: CMC/MICROBIOLOGY	DP: METHOD OF MANUFACTURER		
			INFO AMND: CMC/MICROBIOLOGY	DP: SPECS/ANALYTICAL METHODS		

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
			INFO AMND: CMC/MICROBIOLOGY	DP: STABILITY		
			INFO AMND: CMC/MICROBIOLOGY	DP: FORMULATION		
			INFO AMND: CLINICAL	CLINICAL INCLUSIVE/GENERAL		
			AMND: OTHER	DRAFT PROTOCOL		
			PROTOCOL DISCONTINUED	PROTOCOL		

RESPONDING TO FDA INQUIRIES, GLX AMENDS IND. SPECIFICALLY, GLX CITES PREVIOUS CMC CHANGES FOR D-S, MODIFIES FORMULATION, REVISES/ADDS SPECIFICATIONS/METHODS, SUBMITS RATIONALE (STUDY SUMMARIES) & PROPOSES PROTOCOL SLD-311. ALSO, WITHDRAWS STUDY SLD-201. GLX REQUESTS COMMENT. File Note: Submission subsequently updated with modified CMC tables. Please refer to amendment, Serial #055 dated 9.9.91.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 35239	20		TELECON from FDA to GLAXO	22-FEB-91
IND 35239	34		FAX from FDA to GLAXO	29-APR-91

PROTOCOL	INV#	INVESTIGATOR
SLD-201		
SLD-311		
SLG-H03		
SLG-H08		
SLG-H11		
SLG-H12		
SLG-T02		
SLG-T05		
SLG-T06		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
72	09-SEP-91	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY	C M C INCLUSIVE/GENERAL	3.001-3.001	055

GLX SUBMITS TABLES FROM SECTION I AND II THAT CONVERTED INCORRECTLY DUE TO A SOFTWARE PROBLEM.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 35239	69	052	LETTER from GLAXO to FDA	28-AUG-91

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
117	16-JUN-92	TELECON from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS	MEETING INFO/DETAILS CLINICAL DEVEL PROGRAM	5.001- 5.001	
		MED RVWR NICKLAS CALLS REGARDING 3 MONTH TRIALS BEING CONDUCTED WITH DRY POWDER, ARE THEY "PIVOTAL" TRIALS FOR NDA PURPOSES. NICKLAS STATES GLX SHOULD MEET WITH HIM AND DR LEONARD TO DISCUSS DEVELOPMENT ISSUES IN COMMON WITH INHALATION AEROSOL. POSSIBILITY OF MTG ON 22nd POSSIBLE.				
118	18-JUN-92	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	FDA CONSULT/GUIDANCE	5.001- 5.001	
		CALL MED RVWR NICKLAS REGARDING HIS MTG WITH DR LEONARD. REITERATE INTEREST IN NEW REQUIREMENTS AS GUIDANCE FOR DEVISION MAKING PROCESS REGARDING SLD-312. REQUIREMENTS HAVE BEEN FINALIZED, BUT ARE NOT READY FOR INFORMAL RELEASE, INFO WILL BE AVAILABLE IN SOME MANNER ON 19TH.				
		PROTOCOL INV# INVESTIGATOR SLD-312				
130	23-JUL-92/ 15-JUL-92	LETTER from GLAXO to FDA	REQUESTS/COMMENTS TELECONFERENCE TELECONFERENCE	MEETING INFO/DETAILS CLINICAL INCLUSIVE/GENERAL EFFICACY	5.001- 5.001	
		FOLLOW-UP ON NEW CLINICAL REQUIREMENTS AND ISSUES OF INHALED B2 AGONIST DRUGS. NICKLAS CALLED BACK 21-JUL-92 RE: CONVERSATION WITH LEONARD.				
132	04-AUG-92	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	FDA REVIEW STATUS	5.001- 5.001	
		DR NICKLAS CALLS TO RELAY COMMENTS REGARDING SUBMISSION OF 30-JAN-92 (PTCL SLD-311 FILING).				
		PROTOCOL INV# INVESTIGATOR SLD-311				
135	07-AUG-92/ 04-AUG-92	TELECON from FDA to GLAXO	TELECONFERENCE TELECONFERENCE	CLINICAL INCLUSIVE/GENERAL STATISTICS	5.001- 5.001	

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
			REQUESTS MEETING	ADVISORY CMTE MTG		

DR. NICKLAS CALLS WITH COMMENTS RE: SLG-240 AND SLD-311. RECOMMENDS THAT HOLTER MONITORING BE DONE FOR THESE TWO AND 311 AND 312.GLX INQUIRES ABOUT SCHEDULING SEREVENT FOR ADVISORY COMMITTEE BEFORE THE END OF THE YEAR.

PROTOCOL	INV#	INVESTIGATOR
SLD-240		
SLD-311		
SLD-312		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
141	11-SEP-92	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	CLINICAL INCLUSIVE/GENERAL	5.001-5.001	113

EVEN THOUGH STUDIES COMPLETED, GLX RESPONDS TO COMMENTS FROM FDA MEDICAL REVIEW OF SEVERAL CLINICAL STUDY PROTOCOLS.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
145	02-OCT-92	LETTER from GLAXO to FDA	AGENDA PACKAGE FOR MTG	CLINICAL INCLUSIVE/GENERAL	5.001-	117
			REQUESTS MEETING	CLINICAL INCLUSIVE/GENERAL	5.001	

GLX REQUESTS MEETING TO DISCUSS ISSUES THE FDA MEDICAL REVIEW STAFF WANTED ADDRESSED; GLX ALSO WISHES TO COMBINE THE MEETING REQUEST FOR 21071 AND 30905 WITH THIS ONE.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 21071	141	027	LETTER from GLAXO to FDA	30-JUL-92
IND 30905	361	219	LETTER from GLAXO to FDA	30-JUL-92

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
156	05-NOV-92/ 29-OCT-92	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	UPDATE	6.001-6.001	

GLX MEETS WITH CATHIE SCHUMAKER, SCSO, TO DISCUSS FDA INTERNAL MEETING REGARDING ALTERNATE PROPELLANT ISSUES.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
166	11-DEC-92	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS	6.001-	128
			GENERAL CORRESPONDENCE	DRAFT PROTOCOL	6.001	

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
			GENERAL CORRESPONDENCE	DRAFT LABELING		
		GLX SUBMITS DRAFT PROTOCOL SLD-320 FOR FDA REVIEW FOR 18-DEC-92 MEETING ALONG WITH A LIST OF GLX PERSONNEL ATTENDING MEETING.				
164	15-DEC-92/ 04-DEC-92	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	FDA CONSULT/GUIDANCE	6.001- 6.001	
		GLX MEETS WITH CATHIE SCHUMAKER, SCSO, TO DISCUSS GLX DOING THE SEREVENT POWDER NDA AS A CANDA.				
206	18-DEC-92	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING	CLINICAL INCLUSIVE/GENERAL	6.001- 6.001	158
186	15-MAR-93/ 04-MAR-93	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	UPDATE	7.001- 7.001	
		GLX MEETS WITH CATHIE SCHUMAKER, SCSO, TO DISCUSS PLANS FOR SEREVENT POWDER REGARDING PILOT LAN PROGRAM AT FDA.				
204	06-MAY-93	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY	TOXICOLOGY	7.001- 7.001	157
		GLX SUBMITS SUMMARY OF SALMETEROL/FP TOXICOLOGY STUDIES.				
205	10-MAY-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	RECORD OF UNDERSTANDING	7.001- 7.001	158
		GLX SUBMITS 18-DEC-92 MEETING MINUTES.				
215	28-MAY-93	LETTER from GLAXO to FDA	RESPONSE	PUBLISHED LITERATURE	8.001- 8.001	165

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		GLX SUBMITS REQUESTED LITERATURE REVIEW OF CARDIOVASCULAR INTERACTIONS BETWEEN CORTICOSTEROIDS AND ADRENERGIC AGENTS. FILE NOTE: cover letter only, attachments filed to ind 30905, serial #275.				
		REFERENCE APPLICATION: IND 35239	REFERENCE ACT#: 210	SUP#/ SER#: 157	METHOD OF COMMUNICATION: TELECON from FDA to GLAXO	DOC/ACT DATE: 18-MAY-93
227	03-JUN-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE	FDA CONSULT/GUIDANCE NON-CLINICAL GENERAL	8.001- 8.001	
		GLX SENDS WRITTEN CONFIRMATION OF 03-JUN-93 TELEPHONE CONVERSATION REGARDING SUBMISSION OF COMPLETED NONCLINICAL ALTERNATE PROPELLANT STUDIES.				
228	03-JUN-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE	FDA CONSULT/GUIDANCE NON-CLINICAL GENERAL	8.001- 8.001	
		GLX CONFIRMS AGREEMENT ON HOW GLX WILL SUBMIT FOREIGN NONCLINCIAL STUDIES.				
222	16-JUN-93/ 15-JUN-93	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS INFORMAL DISCUSSIONS	FDA CONSULT/GUIDANCE CLINICAL INCLUSIVE/GENERAL	8.001- 8.001	
		GLX MEETS WITH CATHIE SCHUMAKER, SCSO, TO DISCUSS GETTING FEEDBACK ON CLINICAL PROGRAMS.				
244	09-AUG-93	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	DP: SPECS/ANALYTICAL METHODS	9.001-	
9.001						
		GLX FAXES TO FDA SPECS ON MDPI.				

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
247	23-AUG-93	LETTER from GLAXO to FDA	REQUESTS MEETING REQUESTS MEETING	ELECTRONIC FORMAT FDA CONSULT/GUIDANCE	9.001- 9.001	194

GLX REQUESTS MEETING WITH FDA TO DISCUSS DISKHALER NDA AS CANDA.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
248	23-AUG-93	LETTER from GLAXO to FDA	RESPONSE	SAFETY	9.001- 9.001	

GLX SUBMITS REQUESTED ADDITIONAL INFORMATION REGARDING SAFETY REPORTS.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 35239	238		TELECON from FDA to GLAXO	12-JUL-93/ 08-JUL-93

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
B0000232	RESPONSE		
CGS04271	RESPONSE		
CGS04351	RESPONSE		
G0015320	RESPONSE		
G0015326	RESPONSE		
G0015327	RESPONSE		
G0015328	RESPONSE		
G0016519	RESPONSE		
G0016584	RESPONSE		
G0017043	RESPONSE		
G0017048	RESPONSE		
G0017451	RESPONSE		
G0017490	RESPONSE		
G0017538	RESPONSE		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
249	07-SEP-93	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	ELECTRONIC FORMAT	9.001-	

9.001

GLX REQUESTS COMMENTS ON CANDA SYSTEM PROPOSED 03-SEP-93.

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
255	10-SEP-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS	9.001-	
			GENERAL CORRESPONDENCE	ELECTRONIC FORMAT	9.001	
			GENERAL CORRESPONDENCE	C M C INCLUSIVE/GENERAL		
			GENERAL CORRESPONDENCE	CLINICAL INCLUSIVE/GENERAL		
		GLX SUBMITS LIST OF REQUESTED MEETINGS AND MEETINGS TO BE REQUESTED INCLUDING ONES TO DISCUSS CANDA PROPOSALS, CLINICAL AND CMC ASPECTS OF NDA.				
253	14-SEP-93/ 10-SEP-93	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	CLINICAL INCLUSIVE/GENERAL	9.001- 9.001	
		GLX MEETS WITH DR. POOCHIKIAN, FDA SUPERVISORY CHEMIST, TO REQUEST MEETING TO DISCUSS FDA COMMENT ON PROGRAM.				
258	24-SEP-93	LETTER from GLAXO to FDA	AGENDA PACKAGE FOR MTG	PROTOCOL	10.001-	
			RESPONSE	PROTOCOL	10.001	
		GLX SUBMITS MEETING PACKAGE OF PROTOCOLS SLD-311 AND SLD-312 FOR CANDA MEETING TO CATHIE SCHUMAKER, SCSO.				
		PROTOCOL INV# INVESTIGATOR SLD-311 SLD-312				
259	29-SEP-93	LETTER from GLAXO to FDA	AGENDA PACKAGE FOR MTG	PROTOCOL	11.001-	199
			RESPONSE	PROTOCOL	11.001	
		GLX SUBMITS PROTOCOLS AND SAMPLE CRF FOR SLD-311 AND SLD-312 FOR CANDA MEETING. FILE NOTE: attachments filed with submission to Cathie Schumaker 24-SEP-93.				
		REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		IND 35239	258 LETTER from GLAXO to FDA	24-SEP-93		
		PROTOCOL INV#	INVESTIGATOR			
		SLD-311				
		SLD-312				
267	13-OCT-93	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING	CLINICAL DEVEL PROGRAM	11.001-11.001	
		GLX MEETS WITH FDA REGARDING CMC AND CLINICAL PLANS.				
269	18-OCT-93/ 12-OCT-93	MEETING from GLAXO to FDA	INFORMAL DISCUSSIONS INFORMAL DISCUSSIONS	UPDATE MEETING INFO/DETAILS	11.001-11.001	
		GLX MEETS WITH FDA TO DISCUSS INTENTIONS FOR ROTADISK/DISKHALER AND MEETING AGENDA.				
273	26-OCT-93	LETTER from GLAXO to FDA	AGENDA PACKAGE FOR MTG REQUESTS MEETING REQUESTS MEETING	MEETING INFO/DETAILS MEETING INFO/DETAILS C M C INCLUSIVE/GENERAL	11.001-11.001	203
		GLX REQUESTS MEETING WITH FDA TO DISCUSS CMC SECTION OF ROTADISK NDA AND MDPI TOPICS.				
276	05-NOV-93	LETTER from GLAXO to FDA	RESPONSE	SAFETY	11.001-11.001	
		GLX SUBMITS REQUESTED FOLLOW-UP INFORMATION REGARDING G0017048.				
		MFG CONTROL# ADR PROCESS		REPORT CODE SUBMISSION DATE		
		G0017048 RESPONSE				
279	10-NOV-93	LETTER from GLAXO to FDA	AGENDA PACKAGE FOR MTG AGENDA PACKAGE FOR MTG	MEETING INFO/DETAILS ELECTRONIC FORMAT	11.001-11.001	207
		GLX SUBMITS PRE MEETING PACKAGE FOR 01-DEC-93 CANDA MEETING.				

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
281	12-NOV-93	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY PRTCL AMND: NEW PROTOCOL PRTCL AMND: PROTOCOL CHANGE	DP: MANUFACTURER LABELING INCLUSIVE/GENERAL PROTOCOL PROTOCOL	11.001- 11.001	208

GLX ADDS PROTOCOL SLD-390, EFFECTS OF TWELVE WEEK ROTADISK VS PLACEBO IN AGES 4-11 WITH MILD TO MODERATE ASTHMA, INFO AMENDMENT FOR ALTERNATE PACKAGING AND LABELING OF SUPPLIES, AND AMENDS ENROLLMENT OF SLD-320.

PROTOCOL	INV#	INVESTIGATOR
SLD-320		
SLD-390		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
283	16-NOV-93	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	UPDATE	11.001- 11.001	

GLX SUBMITS DRAFT TABLE OF CONTENTS FOR CANDA FOR FDA MEETING.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
290	24-NOV-93	FAX from FDA to GLAXO	GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE	ELECTRONIC FORMAT FDA CONSULT/GUIDANCE	12.001- 12.001	

FDA FAXES GLX SUGGESTIONS FOR CANDA FUNCTION AND FEATURES NEEDED.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
289	30-NOV-93	LETTER from GLAXO to FDA	RESPONSE	SAFETY	12.001- 12.001	

GLX SUBMITS FDA REQUESTED FOLLOW-UP INFORMATION REGARDING B0001687.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 30905	463		TELECON from FDA to GLAXO	27-SEP-93/ 23-SEP-93

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		B0001687 RESPONSE				
291	30-NOV-93	LETTER from GLAXO to FDA	REQUESTS MEETING	CLINICAL INCLUSIVE/GENERAL	12.001-12.001	212
		GLX REQUESTS MEETING WITH FDA TO DISCUSS ROTADISK NDA SUBMISSION CLINICAL SECTION.				
293	01-DEC-93	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING	ELECTRONIC FORMAT FDA CONSULT/GUIDANCE	12.001-12.001	
		GLX MEETS WITH FDA TO DISCUSS CANDA.				
316	01-DEC-93	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING	ELECTRONIC FORMAT CLINICAL INCLUSIVE/GENERAL STATISTICS SAFETY	12.001-12.001	
		MEETING MINUTES OF 01-DEC-93. PROTOCOL INV# INVESTIGATOR SLD-311 SLD-312				
308	10-DEC-93	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING	DP: IN-PROCESS CONTROLS DP: SPECS/ANALYTICAL METHODS DP: STABILITY	13.001-13.001	
		10-DEC-93 MEETING MINUTES.				
303	13-DEC-93/ 10-DEC-93	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING	DP: IN-PROCESS CONTROLS DP: SPECS/ANALYTICAL METHODS DP: STABILITY	13.001-13.001	
		GLX MEETS WITH FDA TO DISCUSS ROTADISK CMC SECTION OF NDA.				

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
307	17-DEC-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE	DP: IN-PROCESS CONTROLS DP: SPECS/ANALYTICAL METHODS DP: STABILITY	13.001- 13.001	224
		GLX SUBMITS MEETING MINUTES 10-DEC-93.				
315	03-JAN-94	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	RECORD OF UNDERSTANDING	13.001- 13.001	227
		GLX SUBMITS MINUTES OF 01-DEC-93 CANDA MEETING.				
321	10-JAN-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE	FDA CONSULT/GUIDANCE SAFETY	13.001- 13.001	
		GLX FAXES REQUEST FOR UPCOMING NDA SUBMISSION REGARDING SAFETY INFORMATION.				
332	24-JAN-94	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	PROTOCOL	14.001- 14.001	233
		GLX SUBMITS PROPOSAL IN RESPONSE TO FDA REQUEST FOR PROTOCOL AMENDMENT TO SMD-202.				
		PROTOCOL INV# INVESTIGATOR SMD-202				
339	25-JAN-94	LETTER from FDA to GLAXO	RESPONSE RESPONSE	FDA CONSULT/GUIDANCE CLINICAL INCLUSIVE/GENERAL	14.001- 14.001	
		FDA COMPLETES REVIEW OF 18-DEC-92 FDA/GLX CONFERENCE SUMMARY SUBMITTED 10-MAY-93 AND RECOMMENDS GLX PERFORM 3-MONTH EFFICACY STUDY OF THE ALTERNATE PROPELLANT.				

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 35239	205	158	LETTER from GLAXO to FDA	10-MAY-93

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
334	28-JAN-94/ 19-JAN-94	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS INFORMAL DISCUSSIONS	DP: CONTAINER/CLOSURE SYSTEM CLINICAL INCLUSIVE/GENERAL	14.001- 14.001	

GLX MEETS WITH CATHIE SCHUMAKER, SCSO, TO DISCUSS FDA INTERNAL MEETING REGARDING CLINICAL QUESTIONS, AND TO DISCUSS HALF FILL SWITCH.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
344	02-FEB-94	FAX from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS	DP: FORMULATION CLINICAL INCLUSIVE/GENERAL	14.001- 14.001	

CATHIE SCHUMAKER, SCSO, FAXES FDA COMMENTS TO 30-NOV-93 AND 10-JAN-94 PROPOSALS.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 35239	291	212	LETTER from GLAXO to FDA	30-NOV-93
IND 35239	321		FAX from GLAXO to FDA	10-JAN-94

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
349	10-FEB-94	FAX from FDA to GLAXO	REQUESTS/COMMENTS	PROTOCOL	14.001- 14.001	

FDA FAXES COMMENTS TO SMD-202.

PROTOCOL	INV#	INVESTIGATOR
SMD-202		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
357	24-FEB-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	FDA CONSULT/GUIDANCE	14.001- 14.001	

GLX FAXES CATHIE SCHUMAKER, SCSO, MESSAGE TO CALL TO DISCUSS NDA.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
366	07-MAR-94	LETTER from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	MEETING INFO/DETAILS DP: IN-PROCESS CONTROLS DP: SPECS/ANALYTICAL METHODS DP: STABILITY D M F	15.001- 15.001	

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		FDA FINDS 17-DEC-93 MINUTES CONGRUENT EXCEPT AREAS LISTED IN LETTER: CONTROLS TO ASSURE SEGREGATION OF POWDER BLEND, SPECS, IMPURITIES, STABILITY DATA EVALUATION, PERFORMANCE TESTS, BLISTER PACK DMF, AND DATA IN TABULAR FORM.				
		REFERENCE APPLICATION: IND 35239 / REFERENCE ACT#: 307 / SUP#/SER#: 224 / METHOD OF COMMUNICATION: LETTER from GLAXO to FDA / DOC/ACT DATE: 17-DEC-93				
369	25-MAR-94	LETTER from GLAXO to FDA	PRTCL AMND: PROTOCOL CHANGE RESPONSE	PROTOCOL PROTOCOL	15.001- 15.001	249
		GLX SUBMITS AMENDMENT 01 TO SLGA2003 AND COMMENTS TO FDA REQUESTS REGARDING CLINICAL LABS AND MDI ARM.FILE NOTE: attachments filed to IND 43,097 serial #033 only.				
		PROTOCOL: SLGA2003 / INV#: / INVESTIGATOR:				
380	02-MAY-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	UPDATE	15.001- 15.001	
		GLX FAXES CATHIE SCHUMAKER, SCSO, CHART OF UPCOMING PROGRAMS AND SUBMISSIONS.				
378	06-MAY-94	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	SAFETY	15.001- 15.001	
		JOE BUCCINE CALLS TO REQUEST ADDITIONAL INFORMATION REGARDING B0004793.				
		MFG CONTROL#: B0000473 / ADR PROCESS: REQUESTS/COMMENTS / REPORT CODE: / SUBMISSION DATE:				
383	06-JUN-94	LETTER from GLAXO to FDA	RESPONSE	SAFETY	15.001- 15.001	260
		GLX RESPONDS TO FDA REQUEST FOR ADDITIONAL INFORMATION REGARDING B0004793.				

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
386	08-JUN-94	LETTER from GLAXO to FDA	RESPONSE	SAFETY	15.001-15.001	262

REFERENCE APPLICATION: IND 35239 | REFERENCE ACT#: 378 | SUP#/SER#: | METHOD OF COMMUNICATION: TELECON from FDA to GLAXO | DOC/ACT DATE: 06-MAY-94

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
B0004793	RESPONSE		

GLX SUBMITS FOLLOW-UP INFORMATION REGARDING G0012386, B0003182, B0003110, B0002760, AND G0017063.FILE NOTE: attachments filed to IND 30905 serial #359 only.

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
B0002760	RESPONSE		
B0003110	RESPONSE		
B0003182	RESPONSE		
G0012386	RESPONSE		
G0017063	RESPONSE		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
388	24-JUN-94	LETTER from GLAXO to FDA	REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL CLINICAL DEVEL PROGRAM SAFETY	15.001-15.001	264

GLX REQUESTS FDA COMMENTS TO CLINICAL DEVELOPMENT PLAN FOR SEREVENT ROTADISK/DISKHALER.

PROTOCOL	INV#	INVESTIGATOR
SLD-320		
SLGT06		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
392	20-JUL-94	LETTER from GLAXO to FDA	RESPONSE	SAFETY	15.001-15.001	266

GLX SUBMITS FOLLOW-UP INFORMATION REQUESTED ON CGS04271.FILE NOTE: attachments filed to IND

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		30905 serial #365 only.				
		REFERENCE APPLICATION: IND 30905	REFERENCE ACT#: 530	SUP#/SER#: 365	METHOD OF COMMUNICATION: LETTER from GLAXO to FDA	DOC/ACT DATE: 20-JUL-94
		REFERENCE APPLICATION: IND 35239	REFERENCE ACT#: 238		METHOD OF COMMUNICATION: TELECON from FDA to GLAXO	DOC/ACT DATE: 12-JUL-93/ 08-JUL-93
		MFG CONTROL#: CGS04271	RESPONSE	ADR PROCESS	REPORT CODE	SUBMISSION DATE
395	28-JUL-94	LETTER from GLAXO to FDA	INFO AMND: CLINICAL RESPONSE	PROTOCOL PROTOCOL		15.001- 15.001 267
		GLX SUBMITS RESPONSE TO FDA COMMENT/QUESTIONS REGARDING SMD-202.				
		REFERENCE APPLICATION: IND 35239	REFERENCE ACT#: 371	SUP#/SER#	METHOD OF COMMUNICATION: TELECON from FDA to GLAXO	DOC/ACT DATE: 01-APR-94
		PROTOCOL: SMD-202	INV#	INVESTIGATOR		
398	29-JUL-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	SAFETY		15.001- 15.001
		GLX FAXES DR. OTULANA PLANS TO SUBMIT SAFETY UPDATE WITH REFERENCE TO MDI AND LIST WHAT WILL BE INCLUDED.				
396	09-AUG-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	UPDATE		15.001- 15.001
		GLX FAXES FDA DOCUMENTS THAT GLX IS WAITING FOR FDA TO COMMENT ON.				
		REFERENCE APPLICATION	REFERENCE ACT#	SUP#/SER#	METHOD OF COMMUNICATION	DOC/ACT DATE

Application: IND 35239 SEREVENT\ (salmeterol hydroxynaphthoate) Rotadisk

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		IND 35239 388 264	LETTER from GLAXO to FDA	24-JUN-94		
		IND 43097 102	FAX from GLAXO to FDA	01-JUL-94		
397	12-AUG-94/ 11-AUG-94	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	UPDATE	15.001- 15.001	

GLX MEETS WITH PARINDA JANI, CSO, TO DISCUSS LIST OF INTERACTIONS WITH FDA AND GLX AND FOLLOW-UP COMMENTS ON FAXES SENT TO FDA.

400	29-AUG-94	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	SAFETY	15.001-	268
			RESPONSE	SAFETY	15.001	

GLX SUBMITS ANALYSIS OF SERIOUS AE REPORTS OF LARYNGOSPASM OR LARYNGEAL EDEMA.

403	27-SEP-94	LETTER from GLAXO to FDA	RESPONSE	CLINICAL INCLUSIVE/GENERAL	16.001-	271
			RESPONSE	SAFETY	16.001	

GLX SUBMITS RESPONSE TO FDA QUESTIONS REGARDING FORMAT AND CONTENT FOR NDA.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 35239	388	264	LETTER from GLAXO to FDA	24-JUN-94
IND 35239	394		TELECON from GLAXO to FDA	27-JUL-94/ 26-JUL-94
IND 35239	399		TELECON from FDA to GLAXO	22-AUG-94/ 16-AUG-94

PROTOCOL	INV#	INVESTIGATOR
SLD-311		
SLD-312		
SLD-320		
SLGT06		
SLPT02		

409	10-OCT-94	LETTER from GLAXO to FDA	15-DAY WRITTEN ADR REPORT	SAFETY	17.001-	277
			RESPONSE	SAFETY	17.001	

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		GLX RESPONDS TO FDA REQUEST FOR INFORMATION REGARDING B0006051 AND B0004793.				
		MFG CONTROL# B0004793 RESPONSE B0006051 RESPONSE	ADR PROCESS	REPORT CODE	SUBMISSION DATE	
412	31-OCT-94	FAX from GLAXO to FDA	RESPONSE RESPONSE	UPDATE SAFETY	17.001- 17.001	
		GLX SUBMITS SUMMARY OF CURRENT STATUS OF LONG-TERM SAFETY DATA RESPONSE.				
415	08-NOV-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE RESPONSE	DP: FORMULATION DP: FORMULATION	17.001- 17.001	
		GLX FAXES PARINDA JANI, CSO, RATIONALE FOR TWO FORMULATIONS.				
423	09-DEC-94/ 06-DEC-94	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	CLINICAL INCLUSIVE/GENERAL	17.001- 17.001	
		GLX MEETS WITH PARINDA JANI, TO DISCUSS NUMBER OF PATIENTS REQUIRED.				
		PROTOCOL SLD-320	INV#	INVESTIGATOR		
425	13-DEC-94	LETTER from GLAXO to FDA	RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING	CLINICAL INCLUSIVE/GENERAL SAFETY	17.001- 17.001	287
		GLX SUBMITS RECORD OF UNDERSTANDING REGARDING FDA REQUIREMENT FOR LONG-TERM SAFETY DATA.				
434	24-MAR-95	LETTER from GLAXO to FDA	RESPONSE	UPDATE	17.001- 17.001	295
		GLX SUBMITS RESPONSE TO DR. OTULANA'S REQUEST FOR INFORMATION REGARDING SLGA2004				

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		PHARMACOECONOMIC INSTRUMENTS.FILE NOTE: attachments filed to IND 43,097 serial #068 only.				
435	24-MAR-95	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	UPDATE	17.001-17.001	
		GLX FAXES CATHIE SCHUMAKER, SCSO, UPDATED LIST OF PROGRAMS AND ITEM NEEDED FROM FDA.				
453	11-MAR-96	MEETING from GLAXO to FDA	MEETING MEETING	C M C INCLUSIVE/GENERAL CLINICAL INCLUSIVE/GENERAL		
		HIGHLIGHTS FROM THE MEETING HELD WITH FDA REGARDING THE SALMETEROL/FP COMBINATION PRODUCT.				

EXHIBIT 9

Document Chronology / Due Diligence Log

for

IND 43,097

Application: IND 43097 SALMETEROL MDPI

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
1	02-AUG-93	LETTER from GLAXO to FDA	ORIGINAL APPLICATION	C M C DRUG SUBSTANCE INCLUSIVE	1.001-	000
			ORIGINAL APPLICATION	DP: DESCRIPTION	1.001	
			ORIGINAL APPLICATION	DP: IN-PROCESS CONTROLS		
			ORIGINAL APPLICATION	DP: MANUFACTURER		
			ORIGINAL APPLICATION	DP: METHOD OF MANUFACTURER		
			ORIGINAL APPLICATION	DP: PACKAGING PROCESS		
			ORIGINAL APPLICATION	DP: SPECS/ANALYTICAL METHODS		
			ORIGINAL APPLICATION	DP: STABILITY		
			ORIGINAL APPLICATION	ENVIRON IMPACT ASSESSMENT RPT		
			ORIGINAL APPLICATION	DP: FORMULATION		
			ORIGINAL APPLICATION	D M F		
			ORIGINAL APPLICATION	INVESTIGATOR BROCHURE		
			ORIGINAL APPLICATION	CLINICAL DEVEL PROGRAM		
			ORIGINAL APPLICATION	PROTOCOL		
			ORIGINAL APPLICATION	FOREIGN INFORMATION		
			ORIGINAL APPLICATION	PUBLISHED LITERATURE		
			ORIGINAL APPLICATION	MONITOR		
			ORIGINAL APPLICATION	PHARMACOLOGY		
			ORIGINAL APPLICATION	TOXICOLOGY		

GLX SUBMITS ORGINAL APPLICATION FOR SALMETEROL XINAFOATE MULTI-DOSE POWDER INHALER FOR THE TREATMENT AND PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM.

PROTOCOL	INV#	INVESTIGATOR
SMD-200	5165	Grady James
SMD-200		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
3	09-AUG-93	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	DP: CONTAINER/CLOSURE SYSTEM	2.001-	
			GENERAL CORRESPONDENCE	DP: SPECS/ANALYTICAL METHODS	2.001	

GLX SUBMITS DESCRIPTION OF DEVICE.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 43097	2		TELECON from GLAXO to FDA	09-AUG-93/ 03-AUG-93

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
7	12-AUG-93	LETTER from GLAXO to FDA	RESPONSE	DEVICE GENERAL INFORMATION	2.001-	001

Application: IND 43097 SALMETEROL MDPI

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
					2.001	

GLX RESPONDS TO FDA REQUEST AND SUBMITS TWO SAMPLE DEVICES FOR SALMETEROL MULTI-DOSE POWDER INHALER.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 43097	2		TELECON from GLAXO to FDA	09-AUG-93/ 03-AUG-93

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
10	22-AUG-93/ 12-AUG-93	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	DEVICE GENERAL INFORMATION	2.001- 2.001	

GLX MEETS WITH DR. KOBLE, FDA REVIEWING CHEMIST, TO DEMONSTRATE MULIT-DOSE POWDER INHALER DEVICE FROM PATIENT LEAFLET.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
14	07-SEP-93	FAX from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY	DP: IN-PROCESS CONTROLS	2.001- 2.001	

GLX FAXES DR. KOBLE, FDA REVIEWING CHEMIST, INFORMATION REGARDING LEVEL OF DEGRADANT GR97980X.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
20	10-SEP-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE	MEETING INFO/DETAILS C M C INCLUSIVE/GENERAL CLINICAL DEVEL PROGRAM	2.001- 2.001	

GLX SUBMITS LIST OF MEETINGS REQUESTED AND MEETINGS TO BE REQUESTED INCLUDING ONE TO DISCUSS CLINICAL AND CMC DEVELOPMENT PLANS.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
19	14-SEP-93/ 10-SEP-93	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	CLINICAL INCLUSIVE/GENERAL	2.001- 2.001	

GLX MEETS WITH DR. POOCHIKIAN, FDA SUPERVISORY CHEMIST, TO REQUEST MEETING FOR FDA COMMENT ON PROGRAM.

Application: IND 43097 SALMETEROL MDPI

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
23	04-OCT-93	LETTER from GLAXO to FDA	AGENDA PACKAGE FOR MTG	MEETING INFO/DETAILS	2.001-	002
			AGENDA PACKAGE FOR MTG	C M C INCLUSIVE/GENERAL	2.001	
			AGENDA PACKAGE FOR MTG	CLINICAL INCLUSIVE/GENERAL		
		GLX SUBMITS PREMEETING PACKAGE.				
28	06-OCT-93	FAX from FDA to GLAXO	REQUESTS/COMMENTS	DP: IN-PROCESS CONTROLS	2.001-	
			REQUESTS/COMMENTS	DP: SPECS/ANALYTICAL METHODS	2.001	
			REQUESTS/COMMENTS	DP: STABILITY		
		FDA FAXES GLX COMMENTS FROM COMPLETED CHEMISTRY REVIEW.				
29	09-OCT-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	DEVICE GENERAL INFORMATION	2.001-	003
					2.001	
		GLX SUBMITS VIDEO TAPE OF THE HISTORY AND DEVELOPMENT OF THE MULTI-DOSE POWDER INHALER FOR FDA PREPARATION FOR 13-OCT-93 MEETING.				
30	13-OCT-93	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING	DP: IN-PROCESS CONTROLS	2.001-	
			RECORD OF UNDERSTANDING	DP: SPECS/ANALYTICAL METHODS	2.001	
			RECORD OF UNDERSTANDING	DP: STABILITY		
			RECORD OF UNDERSTANDING	CLINICAL DEVEL PROGRAM		
			RECORD OF UNDERSTANDING	PERFORMANCE STANDARDS		
		GLX MEETS WITH FDA REGARDING CMC AND CLINICAL PLANS.				
32	18-OCT-93/ 12-OCT-93	MEETING from GLAXO to FDA	INFORMAL DISCUSSIONS	UPDATE	2.001-	
			INFORMAL DISCUSSIONS	MEETING INFO/DETAILS	2.001	
		GLX MEETS WITH FDA TO DISCUUS RECEIPT OF DEVICE SAMPLES AND MEETING AGENDA.				
36	10-NOV-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	RECORD OF UNDERSTANDING	2.001-	005
					2.001	
		GLX SUBMITS MEETING MINUTES FOR 13-OCT-93 MEETING.				

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38	09-DEC-93	LETTER from GLAXO to FDA	RESPONSE	DP: CONTAINER/CLOSURE SYSTEM	3.001-	007
			RESPONSE	DP: IN-PROCESS CONTROLS	3.001	
			RESPONSE	DP: SPECS/ANALYTICAL METHODS		
			RESPONSE	DP: STABILITY		
		GLX RESPONDS TO FDA CMC COMMENTS FAXED 06-OCT-93 AND SUBMITS CMC AMENDMENT.				
48	10-DEC-93	MEETING from GLAXO to FDA	RECORD OF UNDERSTANDING	DP: CONTAINER/CLOSURE SYSTEM	3.001-	
			RECORD OF UNDERSTANDING	CLINICAL DEVEL PROGRAM	3.001	
			RECORD OF UNDERSTANDING	PERFORMANCE STANDARDS		
		MEETING MINUTES 10-DEC-93.				
40	13-DEC-93/ 10-DEC-93	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	CLINICAL DEVEL PROGRAM	3.001-	
			INFORMAL DISCUSSIONS	DEVICE GENERAL INFORMATION	3.001	
		GLX MEETS WITH DR. KOBLE, FDA REVIEWING CHEMIST, TO PRESENT MINOR MODIFICATIONS TO THE DEVICE.				
43	16-DEC-93	FAX from GLAXO to FDA	RESPONSE	PROTOCOL	3.001- 3.001	
		GLX SUBMITS FDA REQUESTED INFORMATION REGARDING AMENDMENT 01 TO SMD-200.				
		PROTOCOL INV# INVESTIGATOR				
		SMD-200				
47	17-DEC-93	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	DP: CONTAINER/CLOSURE SYSTEM	3.001-	013
			GENERAL CORRESPONDENCE	CLINICAL DEVEL PROGRAM	3.001	
			GENERAL CORRESPONDENCE	PERFORMANCE STANDARDS		
		GLX SUBMITS 10-DEC-93 MEETING MINUTES.				

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63	24-JAN-94	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	PROTOCOL	3.001-3.001	020

GLX SUBMITS PROPOSAL FOR AMENDING SMD-202 IN RESPONSE TO FDA COMMENTS.

PROTOCOL	INV#	INVESTIGATOR
SMD-202		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
82	26-JAN-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	CLINICAL DEVEL PROGRAM	4.001-4.001	

GLX FAXES CATHIE SCHUMAKER, SCSO, LISTING OF MDPI STUDIES COMPLETED, ONGOING AND PLANNED.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
83	02-FEB-94	FAX from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	FDA CONSULT/GUIDANCE CLINICAL INCLUSIVE/GENERAL FOREIGN INFORMATION	4.001-4.001	

FDA FAXES COMMENTS TO 30-NOV-93 AND 10-JAN-94 PROPOSALS.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 35239	344		FAX from FDA to GLAXO	02-FEB-94

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
73	10-FEB-94	FAX from FDA to GLAXO	REQUESTS/COMMENTS	PROTOCOL	4.001-4.001	

FDA FAXES GLX COMMENTS TO SMD-202.

PROTOCOL	INV#	INVESTIGATOR
SMD-202		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
91	06-APR-94	FAX from FDA to GLAXO	REQUESTS/COMMENTS	PROTOCOL	5.001-5.001	

FDA FAXES COMMENTS TO SLGA2004.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 43097	77	027	LETTER from GLAXO to FDA	01-MAR-94

PROTOCOL	INV#	INVESTIGATOR
SLGA2004		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
96	02-MAY-94	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	UPDATE	5.001-5.001	

GLX FAXES CATHIE SCHUMAKER, SCSO, CHART OF UPCOMING PROGRAMS AND SUBMISSIONS.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
100	08-JUN-94	LETTER from GLAXO to FDA	RESPONSE	SAFETY	5.001-5.001	044

GLX SUBMITS FOLLOW-UP INFORMATION REGARDING G0012386, B0003182, B0003110, B0002760, AND G0017063.FILE NOTE: attachments filed to IND 30905 serial #359 only.

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
B0002760	RESPONSE		
B0003110	RESPONSE		
B0003182	RESPONSE		
G0012386	RESPONSE		
G0017063	RESPONSE		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
102	01-JUL-94	FAX from GLAXO to FDA	REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL	5.001-	

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
					5.001	

GLX FAXES DR. OTULANA SUMMARIES OF SLGA2001 AND SLGA2004 FOR COMMENT.

PROTOCOL	INV#	INVESTIGATOR
SLGA2001		
SLGA2004		

107	28-JUL-94	LETTER from GLAXO to FDA	INFO AMND: CLINICAL RESPONSE	PROTOCOL PROTOCOL	5.001- 5.001	046

GLX SUBMITS RESPONSE TO FDA COMMENTS/QUESTIONS REGARDING SMD-202.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 43097	88		TELECON from FDA to GLAXO	01-APR-94

PROTOCOL	INV#	INVESTIGATOR
SMD-202		

113	10-OCT-94	LETTER from GLAXO to FDA	INFO AMND: CLINICAL RESPONSE	SAFETY SAFETY	5.001- 5.001	051

GLX RESPONDS TO FDA REQUEST FOR INFORMATION REGARDING B0004793 AND B0006051.

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
B0004793	RESPONSE		
B0006051	RESPONSE		

125	27-JAN-95	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	CLINICAL DEVEL PROGRAM	6.001- 6.001	063

GLX SUBMITS NEW CLINICAL DEVELOPMENT PROGRAM FOR MDPI RATHER THAN AWAIT FINAL RESULTS OF CURRENT STUDIES FOR COMPARABILITY ANALYSIS.

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
139	22-FEB-95	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS	6.001- 6.001	

GLX FAXES FDA PROPOSED LIST OF ATTENDEES FOR 10-MAR-95 TELECON.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
134	24-MAR-95	LETTER from GLAXO to FDA	RESPONSE	UPDATE	7.001- 7.001	068

GLX RESPONDS TO DR. OTULANA'S REQUEST FOR INFORMATION REGARDING SLGA2004 PHARMACOECONOMIC INSTRUMENTS.

PROTOCOL	INV#	INVESTIGATOR
SLGA2004		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
135	24-MAR-95	FAX from GLAXO to FDA	GENERAL CORRESPONDENCE	UPDATE	7.001- 7.001	

GLX FAXES CATHIE SCHUMAKER, SCSO, UPDATED LIST OF PROGRAMS AND ITEM NEEDED FROM FDA.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 37158	468	208	LETTER from GLAXO to FDA	24-FEB-95

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
137	29-MAR-95	FAX from GLAXO to FDA	RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING	MEETING INFO/DETAILS CLINICAL DEVEL PROGRAM PROTOCOL	7.001- 7.001	

GLX FAXES PARINDA JANI, CSO, DRAFT MINUTES FROM 10-MAR-95 TELECON.

PROTOCOL	INV#	INVESTIGATOR
SLGA2013		
SLGA2014		
SLGA2015		
SLGA2016		
SLGA3009		
SLGA3010		
SLGA3014		

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140	25-APR-95	FAX from GLAXO to FDA	RECORD OF UNDERSTANDING RECORD OF UNDERSTANDING	CLINICAL DEVEL PROGRAM PROTOCOL	7.001- 7.001	
		GLX FAXES FDA MINUTES OF TELECON 03-APR-95.				
146	09-MAY-95	LETTER from GLAXO to FDA	AGENDA PACKAGE FOR MTG GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE	DP: METHOD OF MANUFACTURER DP: STABILITY DP: FORMULATION CLINICAL INCLUSIVE/GENERAL STATISTICS	8.001- 8.001	072
		GLAXO INFORMS FDA THAT ONLY THE SEREVENT MDPI NDA WILL BE PROGRESSED, AND GLAXO WILL NO LONGER PURSUE AN NDA FOR SEREVENT ROTADISK FOR INHALATION. SUBMIT PROPOSED CMC DATA FOR SEREVENT MDPI NDA WITH SUPPORTING DATA FOR SEREVENT ROTADISK. GLAXO ALSO SUBMITS MEETING REQUEST PACKAGE.				
		REFERENCE APPLICATION: IND 43097	REFERENCE ACT#: 136	SUP#/ SER#:	METHOD OF COMMUNICATION: TELECON from GLAXO to FDA	DOC/ACT DATE: 28-MAR-95/ 10-MAR-95
		IND 43097	141		TELECON from GLAXO to FDA	03-APR-95
151	10-MAY-95/ 18-MAY-95	TELECON from GLAXO to FDA	PRE-NDA MTG	MEETING INFO/DETAILS	8.001- 8.001	
		GLAXO TELEPHONES FDA TO CONFIRM THAT THE PROPOSED DATE OF 19-JUL-95 FOR PRE-NDA MEETING WAS ACCEPTABLE.				
145	16-MAY-95	TELECON from GLAXO to FDA	MEETING TELECONFERENCE	MEETING INFO/DETAILS MEETING INFO/DETAILS	8.001- 8.001	
		GLX PHONES FDA TO DISCUSS UPCOMING MEETING TO DISCUSS POST-MARKETING STUDY.				
153	01-JUN-95	TELECON from GLAXO to FDA	PRE-NDA MTG	MEETING INFO/DETAILS	9.001-	

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
			TELECONFERENCE	MEETING INFO/DETAILS	9.001	
		GLAXO TELEPHONES FDA TO DISCUSS ANOTHER DATE FOR THE PRE-NDA MEETING THAT WAS SCHEDULED FOR 19-JUL-95.				
158	22-JUN-95	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS	10.001-10.001	076
		GLAXO SUBMITS MINUTES OF FDA TELECONFERENCES HELD ON 10-MAR-95 AND 03-APR-95				

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 43097	140		FAX from GLAXO to FDA	25-APR-95
IND 43097	157		TELECON from GLAXO to FDA	19-JUN-95

168	16-AUG-95	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS	11.001-11.001	087
		GLAXO SUBMITS MEETING PACKAGE UPDATE TO PREPARE FOR UPCOMING MEETING TO DISCUSS THE PROPOSED NDA.				

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179	31-AUG-95	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	MEETING INFO/DETAILS	11.001- 11.001	
		FDA CALLED TO PROVIDE FEEDBACK ON THE MEETING REQUEST PACKAGE REGARDING THE PRE-NDA MEETING SCHEDULED FOR 18-SEP-95.				
175	06-SEP-95/ 31-AUG-95	TELECON from FDA to GLAXO	RESPONSE	MEETING INFO/DETAILS	11.001- 11.001	
		FDA PROVIDED FEEDBACK ON OUR MEETING REQUEST PACKAGE FOR THE PROPOSED NDA AND INFORMED US THAT THE PACKAGE IS FILEABLE FOR REVIEW.				
174	12-SEP-95	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS	12.001- 12.001	090
		GLAXO PROVIDES TOPICS OF DISCUSSION FOR THE PRE-NDA MEETING.				
185	13-SEP-95	VISIT from GLAXO to FDA	INFORMAL DISCUSSIONS	C M C INCLUSIVE/GENERAL	12.001- 12.001	
		GLAXO DELIVERS DEVICES WITH DESIGN REVISIONS, DEVICE SAMPLES WITH PLACEBO-FILLED STRIPS AND EMPTY FOIL STRIPS, AND INFORMATION REGARDING DEVICE DESIGN CHANGES.				
176	15-SEP-95	TELECON from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS	12.001- 12.001	
		GLAXO CONFIRMED THE FDA ATTENDEES FOR SEREVENT DISKUS PRE-NDA MEETING.				
198	18-SEP-95	VISIT from GLAXO to FDA	INTERNAL COMMUNICATION	MEETING INFO/DETAILS	12.001-	

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			PRE-NDA MTG	C M C INCLUSIVE/GENERAL	12.001	
		GW PROVIDES INTERNAL HIGHLIGHTS OF CMC RELATED DISCUSSIONS DURING THE PRE-NDA MEETING HELD ON 18-SEP-95.				
188	03-OCT-95	FAX from GLAXO to FDA	REQUESTS/COMMENTS	CLINICAL DEVEL PROGRAM	12.001- 12.001	
		GLAXO PANAFAXES OUR PROPOSAL OF KEY STUDIES FOR THE DISKUS NDA.				
194	13-OCT-95	FAX from GLAXO to FDA	RESPONSE	TOXICOLOGY	13.001- 13.001	
		GW PANAFAXES TO FDA A RESPONSE TO THE TOXICOLOGY QUESTIONS RAISED AT THE 18-SEP-95 MEETING ON SEREVENT DISKUS.				
193	17-OCT-95	TELECON from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS	UPDATE TOXICOLOGY	13.001- 13.001	
		FDA CALLS TO COMMENT ON THE TOXICOLOGY INFORMATION THAT HAD BEEN PANAFAXED TO THEM AS A FOLLOW-UP TO THE 18-SEP-95 MEETING ON SEREVENT DISKUS.				

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192	20-OCT-95	LETTER from GLAXO to FDA	RESPONSE RESPONSE RESPONSE	C M C INCLUSIVE/GENERAL CLINICAL INCLUSIVE/GENERAL NON-CLINICAL GENERAL	13.001- 13.001	098
		LETTER TO FDA TO PROVIDE DRAFT MINUTES OF THE 28-SEP-95 MEETING REGARDING THE PROPOSED NDA FOR SEREVENT DISKUS FOR THEIR REVIEW AND COMMENTS.				
218	20-OCT-95	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL	13.001- 13.001	
		GW DISCUSSES THE PROPOSAL FOR THE SEREVENT DISKUS NDA IN REFERENCE TO THE 02-OCT-95 TELEPHONE CONVERSATION. IN ADDITION, GW FAXES PROPOSAL FOR SEREVENT DISKHALER STABILITY DATA TO FDA.				
197	23-OCT-95	FAX from GLAXO to FDA	PRE-NDA MTG PRE-NDA MTG	UPDATE TOXICOLOGY	13.001- 13.001	
		GW PANAFAXES ADDITIONAL TOXICOLOGY INFORMATION TO ASSIST IN THE INTEPRETATION OF LARYNGEAL CHANGES IDENTIFIED IN THE RAT 13-WEEK INHALATION TOXICITY STUDY WITH DEGRADED SALMETEROL IN CONNECTION WITH THE 18-SEP-95 PRE-NDA MEETING.				
199	23-OCT-95/ 19-OCT-95	LETTER from GLAXO to FDA	REQUESTS/COMMENTS TELECONFERENCE	NON-CLINICAL GENERAL TOXICOLOGY	13.001- 13.001	
		GW DISCUSSES ISSUES RELATING TO THE TOXICOLOGY OF GR97980 AND FDA'S QUESTIONS REGARDING THE CHANGES IN THE LARYNX IN ANIMAL STUDIES.				
203	08-NOV-95	FAX from FDA to GLAXO	REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL	13.001- 13.001	
		FDA PANAFAXES THEIR COMMENTS ON STUDY PROTOCOL SLGA3014.				
206	08-NOV-95/ 06-NOV-95	FAX from FDA to GLAXO	REQUESTS/COMMENTS	ELECTRONIC FORMAT	13.001- 13.001	

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		FDA REQUESTS STUDIES (SLD-311, 312, 320; SLGAT06, SLGA2001, 2004, 2006) IN ELECTRONIC FORMAT.				
205	15-NOV-95	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE RESPONSE	PROTOCOL CLINICAL INCLUSIVE/GENERAL	14.001- 14.001	102
		GW SUBMITS RESPONSE TO FDA'S COMMENTS IN THEIR FAX DATED 06-NOV-95 REGARDING PROTOCOL SLGA3014.				
209	28-NOV-95	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	PHARMACOKINETICS	14.001- 14.001	105
		GW PROVIDES FDA WITH A PROPOSAL FOR AN ADDITIONAL STUDY TO STUDY THE PHARMACOKINETICS (TIME TO PEAK AND PEAK PLASMA LEVELS) OF SALMETEROL WHEN ADMINISTERED VIA METERED DOSE INHALER, THE DISKHALER AND DISKUS DEVICES AS REQUESTED BY FDA IN18-SEP-95 PRE-NDA MEETING.				
208	04-DEC-95	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY	NON-CLINICAL GENERAL	14.001- 14.001	106
		GW DISCUSSES THE COMPARISON OF THE SLIDES FROM THE 13 WEEK SEREVENT MDI RAT STUDY (WPT/87/023) AND THE 13 WEEK DEGRADED SEREVENT POWDER STUDY (WPT/89/219) AS SUGGESTED BY THE FDA IN THE 06-NOV-95 TELECONFERENCE AND IN REFERENCE TO THEMEETING HELD ON 18-SEP-95.				
214	21-DEC-95	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE GENERAL CORRESPONDENCE REQUESTS MEETING	CLINICAL DEVEL PROGRAM TOXICOLOGY CLINICAL INCLUSIVE/GENERAL	15.001- 15.001	109
		GW PROVIDES THE TOXICOLOGY PROGRAM THAT IS PLANNED FOR BOTH THE DISKUS INHALER FORMULATION AND THE NON-CFC MDI FORMULATION, THE CLINICAL DEVELOPMENT PROGRAM PLANNED FOR THE DISKUS INHALER FORMULATION, AND REQUESTS A PRE-IND MEETING WITHTHE AGENCY TO REACH AGREEMENT ON OUR DEVELOPMENT PROPOSALS.				

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228	18-JAN-96	FAX from GLAXO to FDA	RESPONSE	NON-CLINICAL GENERAL	15.001-15.001	

GW FAXES TO FDA A LETTER REGARDING OUR PROPOSED 13-WEEK DOG STUDY AND AN OUTLINE FOR THE 13-WEEK DOG STUDY TO COMPARE SALMETEROL POWDER, SALMETEROL POWDER SPIKED WITH GR97980X AND SALMETEROL MDI AS AGREED IN THE 11-JAN-96 TELEPHONE CONVERSATION.

224	24-JAN-96	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	MEETING INFO/DETAILS	15.001-15.001	

FDA CALLS GW TO INFORM US OF THEIR RECEIPT OF THE MEETING REQUEST PACKAGE FOR THE SALMETEROL/FLUTICASONE PROPIONATE COMBINATION PRODUCT AND THAT THEY WOULD LIKE TO MEET ON 11-MAR-96 TO DISCUSS THE PRODUCT DEVELOPMENT PLAN.

226	25-JAN-96	TELECON from GLAXO to FDA	GENERAL CORRESPONDENCE	PHARMACOLOGY	15.001-15.001	

GW CALLS FDA TO DISCUSS THE PROPOSAL FOR A DOG 13 WEEK STUDY THAT HAD BEEN FAXED TO FDA ON 18-JAN-96. FDA AGREED THAT OUR STUDY DESIGN WAS ACCEPTABLE AND REQUESTED THAT THE LOW DOSE OF GR97980X BE RAISED SLIGHTLY TO 0.36 MC/KG.

222	31-JAN-96	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	PUBLISHED LITERATURE	15.001-15.001	

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		FDA REQUESTS A COPY OF THE DRAFT EUROPEAN GUIDELINE ON FIXED COMBINATION PRODUCTS.				
241	11-APR-96	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	DRAFT PROTOCOL	16.001-16.001	121
		INFORM FDA THAT GLX IS WORKING ON THE REVISIONS OF PROTOCOLS SFCA3002 AND SFCA3003. THE REVISIONS WILL BE SUBMITTED IN THE IND.				
		PROTOCOL INV# INVESTIGATOR SFCA3002 SFCA3003				
249	22-MAY-96	FAX from GLAXO to FDA	REQUESTS/COMMENTS	ELECTRONIC FORMAT		
		GW FAXS AN OUTLINE OF THE CLINICAL STUDY REPORT INFORMATION THAT WILL BE PROVIDED IN ELECTRONIC FORMAT FOR THE UPCOMING SEREVENT DISKUS NDA.				
245	23-MAY-96	LETTER from GLAXO to FDA	MEETING MEETING	MEETING INFO/DETAILS CLINICAL DEVEL PROGRAM		124
		GW SUBMITS DRAFT MINUTES OF THE 11-MAR-96 MEETING TO DISCUSS THE DEVELOPMENT PLAN FOR THE SALMETEROL/FLUTICASONE PROPIONATE COMBINATION PRODUCT.				

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247	23-MAY-96	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS		124
		GW PROVIDES MINUTES OF THE 11-MAR-96 MEETING TO DISCUSS THE SALMETEROL/FLUTICASONE PROPIONATE COMBINATION PRODUCT. THIS LETTER INCORRECTLY INDICATED "DRAFT" MINUTES IN THE RE: SECTION; HOWEVER, PER TELEPHONE CONVERSATION WITH FDA, P. JANIHAS AGREED TO CROSS-OUT THE WORD "DRAFT".				
253	05-AUG-96	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	CLINICAL DEVEL PROGRAM		128
		Detailed analysis plan for quality of life program in asthmatic adult and adolescent patients receiving salmeterol MDPI.Request to FDA for discussion of this proposal concerning quality of life claims and our plans for this product.				
259	27-AUG-96	LETTER from GLAXO to FDA	MEETING	MEETING INFO/DETAILS		
		GENERAL CORRESPONDENCE REGARDING THE SUBMISSION OF 20-692. A MEETING IS REQUESTED TO DISCUSS DETAILS.				
260	27-AUG-96	LETTER from GLAXO to FDA	MEETING	MEETING INFO/DETAILS		
		REQUEST FOR A MEETING WITH THE AGENCY TO GO OVER THE DETAILS OF SUPPLEMENTAL APPLICATIONS.				
257	03-SEP-96	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	CLINICAL		
		GENERAL CORRESPONDENCE ABOUT MEETING TO DESCRIBE THE ELECTRONIC LUNG IN MORE DETAIL THAN WHAT WAS PROVIDED.				
258	27-SEP-96	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	CLINICAL STUDY STATUS		

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		CLINICAL REPORT FOR SFCB1002.				
265	29-OCT-96	LETTER from GLAXO to FDA	PRE-NDA MTG	MEETING INFO/DETAILS		
		Corrections to Serial No. 130, submitted August 27, 1996 and overheads for possible use at 11/4/96 meeting.				
266	01-NOV-96	LETTER from GLAXO to FDA	PRE-NDA MTG	MEETING INFO/DETAILS		
		Parinda called to request that the meeting time be modified to 1:00 for the FDA teleconference for Pre-sNDA meeting.				
268	06-NOV-96	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	CLINICAL INCLUSIVE/GENERAL		
		Final clinical report for SMDT10. It is not being submitted to the pending NDA since we are not seeking to include comparative data in the package insert for Servent Diskus.				
269	19-NOV-96	LETTER from GLAXO to FDA	RECORD OF UNDERSTANDING	RECORD OF UNDERSTANDING		
		Minutes to 11/4/96 teleconferences on Serevent Diskus sNDAs for Pediatric Asthma, Health Related Quality of Life and Exercise Induced Bronchospasm.				
274	03-DEC-96	LETTER from GLAXO to FDA	RECORD OF UNDERSTANDING	RECORD OF UNDERSTANDING		
		FDA minutes of 11/4/96 pre-sNDA teleconference for Serevent Diskus Pediatric Asthma, exercise-induced Bronchospasm and Health related Quality of Life.				
275	16-JAN-97	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	CLINICAL INCLUSIVE/GENERAL		

Application: IND 43097 SALMETEROL MDPI

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		Provided information on the statistical methods used for the QOL data in study SLGA originally filed on October 13, 1995 (serial #097).				
276	31-JAN-97	LETTER from GLAXO to FDA	PRE-NDA MTG	MEETING INFO/DETAILS		
		Follow-up on Pre-sNDA Meeting. Study summaries for FDA's evaluation and decision on if they must be included in the pediatric asthma or EIB supplemental NDAs to NDA 20-692.				
280	21-FEB-97	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	PROTOCOL		
		Susan Johnson agrees that we may leave SMDT10 and SLGT29 out of the pediatric and EIB supplements and report them vis the annual report mechanism.				
284	11-MAR-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	CASE REPORT TABULATIONS		
		Teleconference to discuss GW's request to submit SLGA3010 and 3011 without case report form tabulations in the upcoming Serevent Diskus sNDAs.				
286	04-APR-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	UPDATE		
		Left a voice mail message with P. Jani stating that GW did wish to discuss with FDA the possibility of seeking EIB and pediatric indications as stand alone NDAs.				
287	08-APR-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	UPDATE MEETING INFO/DETAILS SAFETY		
		Discussed the possibility of submitting the pediatric and EIB indications as stand alone NDAs and GW's proposal to submit the pediatric safety data in the pediatric NDA only (leaving it				

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		out of the final safety update).FDA requested list of GW's attendees of the 4/4/97 teleconference.				

EXHIBIT 10

Document Chronology / Due Diligence Log

for

NDA 20-692

Application: NDA 20692 Serevent (salmeterol xinafoate) Diskus Inhalation Powder

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
17	18-JUN-96	LETTER from GLAXO to ONCOLOGY/ PULMONARY	ORIGINAL APPLICATION	ADMINISTRATIVE		
		Original submission of NDA: Serevent(r) Diskus(r) Inhalation Powder. Indication: maintenance treatment of asthma and the prevention of bronchospasm in patients 12-years-old and older with reversible obstructive airway disease.				
19	02-JUL-96	LETTER from GLAXO to ONCOLOGY/ PULMONARY	REQUESTS/COMMENTS	ADMINISTRATIVE		
		Delivery of desk copies of certain volumes for reviewers.				
2	03-JUL-96	LETTER from ONCOLOGY/PULMONARY to GLAXO	ORIGINAL APPLICATION	UPDATE		
		Confirmation that FDA has received the original NDA on June 19, 1996, and that the filing date is August 18, 1996.				
1	12-JUL-96	LETTER from GLAXO to ONCOLOGY/ PULMONARY	REPORT REQUEST	UPDATE		
		Submitted replacement page for Vol 150, page 484 in original submission.				
34	21-JUL-96	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL		
		CLINICAL-ACCEPTABILITY OF CRF TABULATION PROPOSAL.				
24	25-JUL-96	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	ELECTRONIC FORMAT		
		FDA CALLS TO REQUEST APPENDIX TABLES IN THE ELECTRONIC VERSIONS OF PREVIOUSLY SUBMITTED REPORTS.				

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
35	16-AUG-96	LETTER from GLAXO to FDA	RESPONSE	UPDATE		
		120 DAY SAFETY UPDATE.				
23	06-SEP-96	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	SAFETY		
		FDA REQUESTS MORE DETAIL ABOUT THE CONTENTS OF THE 120-DAY SAFETY UPDATE.				
37	06-SEP-96	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	PATIENT DATA		
		INFORMATION REQUEST ON THE CLINICAL DEFINITION OF "PACK HISTORY" AS IT RELATES TO THE SMOKING HABITS OF PATIENTS.				
20	10-SEP-96	LETTER from GLAXO to FDA	RESPONSE RESPONSE	CLINICAL INCLUSIVE/GENERAL SAFETY		
		GW PROVIDES CLINICAL AND ADVERSE EVENTS INFORMATION REGARDING PROTOCOLS SLD-312, SLGA2001, AND SLGA2004 FOR THE PURPOSE OF CONDUCTING CLINICAL INSPECTIONS.				
22	12-SEP-96	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	LABELING INCLUSIVE/GENERAL		
		FDA CALLS TO SUGGEST 04-NOV-96 AS A DATE FOR THE PEDIATRIC ASTHMA, EXERCISE-INDUCED BRONCHOSPASM AND QUALITYN OF LIFE WORDING MEETING.				
21	16-SEP-96	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	LABELING INCLUSIVE/GENERAL		
		GW CALLS FDA TO REQUEST A PRE-SDNA PEDIATRIC ASTHMA, EXERCISE-INDUCE BRONCHOSPASM MEETING FOR 04-NOV-96.				

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
28	17-SEP-96	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	RECORD OF UNDERSTANDING		
		COMMENT/REQUEST FOR ADDITIONAL COPIES OF PRE-MEETING PACKAGE.				
27	20-SEP-96	LETTER from GLAXO to FDA	RESPONSE	UPDATE		
		RESPONSE FOR ADDITIONAL INFORMATION ON THE MANUFACTURING AND STABILITY TESTING SITES.				
31	23-SEP-96	LETTER from GLAXO to FDA	PRE-IND MTG	MEETING INFO/DETAILS		
		LETTER ABOUT A PREIND MEETING.				
44	23-SEP-96	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	STABILITY PROTOCOL		
		REQUEST BY RICK LOSTRITTO TO THE STABILITY TESTING OF UNMICRONIZED ND MICRONIZED DRUG SUBSTANCE.				
26	27-SEP-96	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	CLINICAL STUDY STATUS		
		CLINICAL REPORT FOR SFCA1001 AND SFCB1002.				
46	04-OCT-96	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	STABILITY PROTOCOL		
		REQUEST FOR THE LOCATION OF THE BATCH RECORDS FOR THE STABILITY, PRODUCTION, AND KEY CLINICAL STUDIES. PROVIDED WERE VOLUME NUMBERS AND PAGES FROM THE NDA.				
40	08-OCT-96	LETTER from GLAXO to FDA	PRE-NDA MTG	EFFICACY		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		PRE-NDA MEETING AGREED TO USE DATA FROM US STUDIES ON THE REDUCED FILL FORMULATION TO SUPPORT PIVOTAL EFFICACY DATA.				
41	08-OCT-96	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY	TOXICOLOGY		
		FINAL REPORT FOR STUDY D21268:13 WEEKS INHALATION TOXICITY STUDY IN DOGS.				
43	21-OCT-96	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY	C M C INCLUSIVE/GENERAL		
		REFERENCE IS MADE TO THE AGENCY'S REQUEST OF SEPTEMBER 18, 1996 FOR ADDITIONAL INFORMATION ON THE MANUFACTURING AND STABILITY TESTING SITES OF SEREVENT DISKUS FOR WHICH A RESPONSE WAS SUBMITTED ON SEPT 20, 1996.				
48	21-OCT-96	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	MEETING INFO/DETAILS		
		FACSIMILE TRANSMISSION OF LIST OF GLAXO WELLCOME ATTENDEES FOR 11/4/96 MEETINGS TO DISCUSS SNDAS FOR PEDIATRIC ASTHMA, HRQL, AND EIB.				
51	21-OCT-96	LETTER from GLAXO to FDA	MEETING	MEETING INFO/DETAILS		
		LIST OF GW ATTENDEES FOR 11/4/96 MEETINGS TO DISCUSS SNDAS FOR PEDIATRIC ASTHMA, HRQL, AND EIB.				
50	25-OCT-96	LETTER from GLAXO to FDA	RESPONSE	NON-CLINICAL GENERAL		
		RESPONSE TO THE REQUEST OF 10/23 REGARDING THE 13 WEEK DOG STUDY.				
53	05-NOV-96	LETTER from GLAXO to FDA	PRE-NDA MTG	MEETING INFO/DETAILS		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		Follow-up to User Fee question from Pre-sNDA Meeting to discuss pediatric asthma and exercise induced Bronchospasm.				
54	06-NOV-96	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Request (CMC) for location of cascade impaction data by Stage.				
55	12-NOV-96	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	MEETING INFO/DETAILS		
		Informaton request-Pre-Approval inspection contact person and scheduling.				
126	14-NOV-96	LETTER from GLAXO to FDA	MEETING	MEETING INFO/DETAILS		
		Request for a meeting to present and discuss with the Agency our DPI development strategy.				
56	19-NOV-96	LETTER from GLAXO to FDA	RECORD OF UNDERSTANDING	RECORD OF UNDERSTANDING		
		Minutes to 11/4/96 teleconference on Serevent Diskus Supplemental NDAs for pediatric asthma, health related quality of life and exercise induced bronchospasm.				
59	22-NOV-96	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	ELECTRONIC FORMAT		
		With regard to the October 16, 1996 telephone conversation with Dr. Lostritto, we are submitting a videotape entitled "An introduction to the MDPI Manufacturing Process" which illustrates the manufacturing process described in the SereventPowder NDA submitted on June 18, 1996. This film, describes the basic manufacturing techniques described in the application.				

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
60	03-DEC-96	LETTER from GLAXO to FDA	RECORD OF UNDERSTANDING	RECORD OF UNDERSTANDING		
		FDA minutes of 11/4/96 pre-sNDA teleconference for Serevent Diskus Pediatric Asthma, exercise-induced Bronchospasm and Health related Quality of Life.				
61	16-DEC-96	LETTER from GLAXO to FDA	RESPONSE	DEVICE GENERAL INFORMATION		
		Submitted Serevent Diskus sample devices containing placebo strips without the foil overwrap.				
64	14-FEB-97	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Deficiencies of the CMC section of the submission dated September 20, October 21 and November 19, 1996.				
67	20-FEB-97	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	C M C INCLUSIVE/GENERAL		
		Reference is made to NDA 20-692 orginally submitted June 18, 1996, and to review comments received by the chemistry reviewer on February 14, 1997. Assessing the review comments and do not yet have a firm estimate for the response date.				
72	28-FEB-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Discussion with Rick Lostritto, Reviewing Chemist, to discuss the response timings to the Serevent Deficiency questions received February 14, 1997.				
68	03-MAR-97	LETTER from GLAXO to FDA	MEETING	MEETING INFO/DETAILS		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		Request for a teleconference to dicuss and clarify questions in the February 20, 1997 letter.				
74	20-MAR-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS TELECONFERENCE	DP: STABILITY C M C INCLUSIVE/GENERAL		
		Teleconference was held to clarify deficiency questions received from the Agency on February 14, 1997.				
75	21-MAR-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS	DP: STABILITY DS: IN-PROCESS CONTROLS		
		R. Lostritto called to continue the teleconference held on 3/20/97. Discussed deficiency questions received from the Agency on 2/14/97.				
78	01-APR-97	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY	DP: MANUFACTURER		
		The purpose of this submission was to amend Section D, Manufacturer(s), D1, to include GW Operations, Dartford, UK as the site of microbiological testing and to add Bldg. S (blending process) to the Glaxo Operations UK Ltd., Ware UK site.				
81	03-APR-97	FAX from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL STATISTICS		
		Provided clinical questions/comments and requested a response no later than 4/25/97.				
82	04-APR-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	UPDATE		
		Left a voice mail message stating that GW wished to discuss with FDA the possibility of seeking the EIB and pediatric indications as stand alone NDAs.				
84	08-APR-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	UPDATE		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
			REQUESTS/COMMENTS	MEETING INFO/DETAILS		
			REQUESTS/COMMENTS	SAFETY		
		Spoke with P. Jani regarding the possibility of submitting the pediatric and EIB indications as stand alone NDAs and our proposal to submit the pediatric safety data in the pediatric NDA only (leaving it out of the final safety update).Ms. Jani requested a list of attendees of the CMC teleconference held on 4/4/97.				
85	09-APR-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	DP: IN-PROCESS CONTROLS		
			REQUESTS/COMMENTS	TOX: MUTAGENICITY		
		Dr. Sancilio called and asked for clarification related to the percent impurity in the drug product used in the mutagenicity study.				
86	10-APR-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	DP: IN-PROCESS CONTROLS		
			REQUESTS/COMMENTS	TOX: MUTAGENICITY		
		Provided clarification of the percent impurity in the drug product used in the mutagenicity study.				
89	17-APR-97	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
			REQUESTS/COMMENTS	DP: STABILITY		
		Responded to CMC questions received February 14, 1997. Also updated the stability data for the three production batches of Serevent Diskus 50mcg in the proposed blister packaging materials with foil laminate overwrap.				
90	21-APR-97	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL		
		Submitted formal response to the comments/requests outlined in the Agency's letter dated April 3, 1997.				
93	30-APR-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		Called Rick Lostritto to discuss comment 9c of the Feb. 14, 1997 comments from FDA.				
92	08-MAY-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	CLINICAL STUDY STATUS		
		Parinda Jani called to inquire about the status of SLGA3009.				
98	15-MAY-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Called Rick Lostritto to inform him that the proposal requested on May 14, 1997 on the common CMC issues related to the Serevent Diskus and Flovent Rotadisk NDAs had been faxed to him. (copy of the fax is attached).				
99	21-MAY-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Called Rick Lostritto to continue discussions around the additional questions to the April 17, 1997 submission.				
100	23-MAY-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Teleconference to provide verbal responses to the 9 questions that the Agency had as a result of reviewing the April 17, 1997 responses to the Serevent Diskus Feb. 14, 1997 comments.				
101	30-MAY-97	LETTER from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Provided complete responses to the outstanding CMC comments received from the Agency 2/14/97.				
102	02-JUN-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		Delivered the Phase II responses to FDA. Also briefly met with Rick Lostritto, Reviewing Chemist, to review the responses.				
103	06-JUN-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS REQUESTS/COMMENTS TELECONFERENCE	C M C INCLUSIVE/GENERAL DP: SPECS/ANALYTICAL METHODS FDA REVIEW STATUS		
		Agency called to request additional information on the mouthpiece extractives test referenced in GWs response to Question 27 submitted to the Agency on 5/30/97.				
104	09-JUN-97	FAX from GLAXO to FDA	RESPONSE	DP: SPECS/ANALYTICAL METHODS		
		As requested by the Agency in a telephone conversation on 6/6/97, GW provided via facsimile, revised specifications for the drug product.				
107	12-JUN-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	FDA REVIEW STATUS		
		Discussed status of FDA review of the NDA. The Review Team at the Agency will be recommending to Dr. Jenkins that the review clock be extended to Sept. 18, 1997.				
106	16-JUN-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	PATIENT DATA		
		Requested location of the case report forms for SLD-320 in the 120-day safety update.				
108	20-JUN-97	FAX from FDA to GLAXO	REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL		
		Facsimile from the Agency regarding clinical comments on pending NDA 20-692.				
109	25-JUN-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		GW called to request clarification on three of the CMC comments of the June 19, 1997 correspondence from FDA, specifically comments 3,6, and 8.				
118	07-JUL-97	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	LABELING INCLUSIVE/GENERAL		
		P. Jani called and left a message that the fax GW had submitted to the Agency with the revised figures for the estimated human exposure multiples (based on animal studies data) were acceptable. (Reference S-014).				
117	18-JUL-97	TELECON from GLAXO to FDA	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL		
		Called the Agency to give them an update on the response to the June 19, 1997 CMC comments received via facsimile from the Agency.				
121	22-JUL-97	LETTER from GLAXO to FDA	RESPONSE	C M C INCLUSIVE/GENERAL		
		Provided complete responses to the June 19, 1997 facsimile which provided the Agency's comments to GW's April 17, 1997 submission.				
124	24-JUL-97	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	NAME CHANGE		
		Submitted request for review of a new proprietary name, Serevent Breeze Inhalation Powder and an alternate name of Serevent Accuhaler Inhalation Powder.				
125	25-JUL-97	LETTER from GLAXO to FDA	RESPONSE	CLINICAL INCLUSIVE/GENERAL		
		Provided responses to the Agency's comments/requests outlined in the Agency's letter of June 20, 1997.				

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ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
129	24-AUG-97	LETTER from GLAXO to FDA	RESPONSE	STABILITY PROTOCOL		

Describing and providing supportive in-vitro comparability data for two minor device refinements. Provides stability data for up to 9 months storage.